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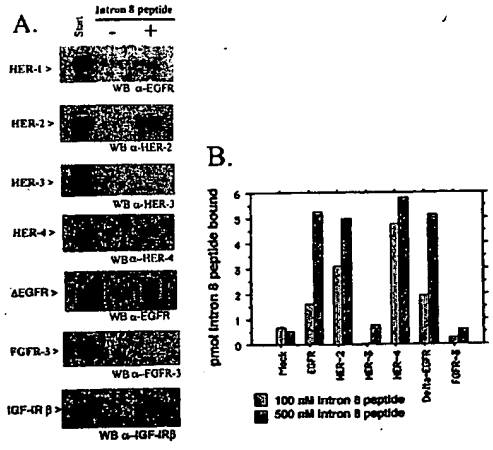
(54) Title: COMPOSITIONS AND METHODS FOR MODULATING SIGNALING MEDIATED BY IGF-1 RECEPTOR AND ERBB RECEPTORS



(57) Abstract: The binding interactions between herstatin, or the intron 8-encoded receptor binding domain (RBD Int8) thereof, and several receptors were analyzed. According to aspects of the present invention, herstatin and the intron 8-encoded domain bind with high affinity (e.g., nM concentrations) to all four of the ErbB receptors: EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); and HER-4 (erbB-4), as well as to ?EGFR and the IGF-1 receptor, and such binding has utility to modulate signaling mediated by these receptors. Herstatin inhibited target receptor-mediated activation of intracellular signaling pathways ((e.g., PI3/Akt, IRS-2, etc., pathways) that are important in cell survival, and further inhibited target receptor-mediated (e.g., IGF-1/IGF-1R-mediated) survival of cancer cells. Aspects of the present invention thus provide methods and compositions for the treatment of cancer, including cancer refractory to other erbB-based agents, and of other conditions and disorders characterized by target receptor expression, over-expression, signaling, and/or aberrant signaling. Additional aspects provide methods of targeted drug delivery.

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COMPOSITIONS AND METHODS FOR MODULATING SIGNALING MEDIATED BY IGF-1 RECEPTOR AND ERBB RECEPTORS

FIELD OF THE INVENTION

This invention relates generally to signaling through IGF-1 receptors and through ErbB family member receptors, and more specifically to novel methods and compositions for modulating intracellular signaling mediated by IGF-1 receptor and by ErbB family receptors, for cell targeting, and for the treatment of cancer and other target receptor-mediated conditions and disorders.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional Patent Application Serial Number 60/590,473, filed 23 July 2004, and entitled COMPOSITIONS AND METHODS FOR TREATING CANCER BY MODULATING IGF-1 RECEPTOR AND ERBB RECEPTORS, to United States Provisional Patent Application Serial Number 60/564,893, filed 22 April 2004, of same title, both of which are incorporated by reference herein in their entirety.

STATEMENT REGARDING FEDERALLY-SPONSORED RESEARCH

This work was partially funded by NIH grant number CA83503, and the United States government has, therefore, certain rights to the present invention.

BACKGROUND

The ErbB receptor family consists of four receptor tyrosine kinases: EGFR (HER-1, erbB-1), HER-2 (erbB-2), HER-3 (erbB-3) and HER-4 (erbB-4). Aberrant expression of ErbB receptors by mutational activation, receptor overexpression, and tumor production of ligands contributes to the development and maintenance of a variety of human cancers (*e.g.*, Olayioye et al., *Embo J.*, 19:3159-67, 2000).

The ErbB receptors, with one exception, are activated by several ligands with an EGF core domain (EGF-related growth factors). HER-2 receptor, the exception, is recruited as a preferred dimer partner with other ligand-binding erbB receptors (*Id*). The eleven mammalian

EGF-like ligands are all agonists, whereas *Drosophila* has the ligand 'Argos' that inhibits activation of the EGFR (Dougall et al., *Oncogene* 9:2109-23, 1994; Hynes & Stern, *Biochim. Biophys. Acta* 1198:165-84, 1994; Tzahar & Yarden, *Biochim. Biophys. Acta* 1377:25-37, 1998).

Although the HER-2 receptor does not directly bind EGF-like ligands, a secreted product of an HER-2 alternative transcript, herstatin, binds with high affinity ($K_D \cong 14$ nM) to the ectodomains of HER-2 and the EGF receptor (EGFR). Herstatin consists of a segment of the HER-2 ectodomain (340 amino acids that are identical to the N-terminal subdomains I and II), followed by 79 amino acids encoded by intron 8 of the HER-2 gene that function as a receptor binding domain (RBD) (Doherty et al., *Proc. Natl. Acad. Sci. USA* 96:10869-74, 1999). Herstatin blocks homomeric and heteromeric ErbB receptor interactions, inhibits activation of the PI3K/Akt pathway initiated by EGF, TGFα, and Heregulin, causes growth arrest, and has substantial utility as an anti-cancer agent (*Id*, and see, *e.g.*, Azios et al., *Oncogene* 20:5199-209, 2001; Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003; and Justman & Clinton, *J. Biol. Chem.* 277:20618-24, 2002).

Anti-erbB receptor antibody agents, such as the HER-2-specific antibody rhuMAb4D5 (HERCEPTIN™) have been approved for cancer therapy. Significantly, however, tumor cells may be inherently resistant, or gain resistance, to anti-erbB receptor therapies through activation of IGF-IR pathways (see, *e.g.*, Chakravarti et al., *Cancer Res.* 62:200-7, 2002 (discussing IGF-1R-mediated resistance to AG1478, an EGFR tyrosine kinase inhibitor); Lu et al., *J. Biol. Chem.* 279:2856-65, 2004; Lu et al., *J. Natl. Cancer Inst.*, 93:1852-7, 2001 (discussing IGF-1R-mediated resistance to Herceptin™, in the context of breast cancer); and Camp, 2005 (discussing IGF-1R-mediated resistance to Iressa, a small molecule EGFR inhibitor, in the context of breast and prostate cancer)). Activation of the IGF-I receptor (IGF-IR) by IGF-I promotes, *inter alia*, proliferation, survival, transformation, metastasis, and angiogenesis (see, *e.g.*, Baserga, *Hum. Pathol.* 31:275-6, 2000; and Wang & Sun, *Curr. Cancer Drug Targets* 2:191-207, 2002), and signaling through both IGF-IR and EGF receptors is central to tumorigenesis.

There is, therefore, a pronounced need in the art not only to further investigate and characterize the interactions among the erbB family receptors, but to identify modulators of the signaling mediated by erbB receptors and IGF-1 receptors. There is a need in the art for a multi-

functional inhibitor that *simultaneously* targets both the EGF and IGF-IR families. There is a pronounced need in the art to identify and develop modulators (*e.g.*, inhibitors) of erbB receptors and of IGF-IR modulators as therapeutic agents (*e.g.*, anti cancer agents). There is a need in the art to further assess the receptor-modulating utilities of herstatin and its intron 8-encoded RBD.

SUMMARY OF THE INVENTION

According to particular aspects of the present invention, herstatin, and the intron 8-encoded domain thereof (referred to herein as "int8 RBD"), bind with high affinity (*e.g.*, at nM concentrations) to: all four of the ErbB receptors EGFR (HER-1, erbB-1), HER-2 (erbB-2), HER-3 (erbB-3), and HER-4 (erbB-4); as well as to ΔEGFR and the IGF-1 receptor. Moreover, such target receptor binding has been shown and disclosed herein to have novel and substantial utility to modulate intracellular signaling mediated by these receptors.

Particular embodiments provide novel methods and compositions for the treatment of cancer and other conditions and disorders characterized by target receptor expression or over-expression, and/or target receptor mediated signaling or aberrant signaling.

Specific embodiments provide a method for treating cancer, comprising administering a therapeutically effective amount of herstatin, or of a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors. Alternatively, a therapeutically effective amount of a Int8 RBD polypeptide, or of a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, is administered. The methods also encompass treatments where the cancer cells further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

Further embodiments provide combination therapies, further comprising, administration of a therapeutically effective amount of: a receptor-specific antibody that binds to the extracellular domain of a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-1R; or of a chemotherapeutic (*e.g.*, anti-neoplastic) agent.

Additional embodiments provide pharmaceutical compositions for treating cancer and other conditions and disorders characterized by target receptor expression or over-expression, and/or target receptor-mediated signaling or aberrant signaling, comprising, along with a pharmaceutically acceptable diluent, carrier or excipient, herstatin, or a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4); IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors. Alternatively, the inventive compositions comprise, along with a pharmaceutically acceptable diluent, carrier or excipient, a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors.

The compositions also have substantial utility in treatments where the target cells (*e.g.*, cancer cells) further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

Additional aspects provide novel methods of targeted drug delivery.

Specific embodiments provide methods for targeting a therapeutic agent to cancer cells, comprising attaching the therapeutic agent to herstatin, or to a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4); IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors. Alternatively, the therapeutic agent is attached to a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4); IGF-r and combinations thereof, wherein the cancer cells express at least one of the target receptors.

The targeting methods encompass treatments wherein the cancer cells further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

Preferably, for the above-described methods and compositions, the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present. Preferably, the herstatin, or variant thereof,

further comprises at least one N-linked glycosylation site, and binds to the extracellular domain of EGF receptor with an affinity binding constant of at least about 10^7 M^{-1}, or of at least about 10^8 M^{-1}.

Preferably, for the above-described methods and compositions, the Int8 RBD polypeptide, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length. Preferably, the Int8 RBD polypeptide, or variant thereof binds to the extracellular domain of target receptor with an affinity binding constant of at least about 10^7 M^{-1}, or of at least about 10^8 M^{-1}.

Additional embodiments provide for a novel form of HER-3 (SEQ ID NO:14) that does not bind to herstatin or to Int8 RBD polypeptides, thus providing screening assays for cells having impaired responsiveness to herstatin or int8 RBD polypeptides.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A demonstrates that the RBD Int8 polypeptide, purified from bacteria and immobilized on Protein S Sepharose™ 'pulled down' IGF-IR from 3T3 cell extracts.

Figure 1B illustrates a binding curve showing saturable binding by the RBD Int8 polypeptide that is specific for IGF-IR.

Figure 1C illustrates the results of ELISA assays showing that herstatin, purified from transfected S2 insect cells, exhibited dose-dependent binding to IGF-1R at nM concentrations.

Figure 1D illustrates binding curves showing that full-length herstatin exhibited saturation binding to IGF-IR 3T3 cells, demonstrating nM binding affinity.

Figures 2A and 2B show that herstatin prevented activation of IGF-1R by IGF-1 in MCF-7 cells. Figure 2A shows a representative Western immunoblot of IGFI-R immunoprecipitation of IGF-I-treated MCF-7 and MCF-7/Hst cell lysates. Figure 2B shows a graphical representation of two independent experiments of IGF-I-induced activation of the IGF-I receptor. The lower portion of Figure 2A shows that herstatin not only prevented activation of IGF-1R by IGF-1 in MCF-7 cells, but also caused down-regulation of IGF-1R.

Figure 3A shows, using 'pull-down' assays, that the herstatin RBD Int8 polypeptide

bound in a specific manner to EGFR, HER-2, HER-4, IGF-1R and ΔEGFR, but did not bind to a mutant form of HER-3, to FGFR-3, or to mock-transfected cells.

Figure 3B shows, using ELISA, that the Int8 polypeptide bound in a specific and dose-dependent manner to EGFR, HER-2, HER-4, and ΔEGFR, but not to a mutant form of HER-3, FGFR-3, or mock-transfected cells.

Figures 4A and 4B illustrate Western blot analyses of RBD Int8 polypeptide binding to different forms of HER-3: Figure 4A shows lack of RBD Int8 polypeptide binding to a form of HER-3 having a single point mutation resulting in substitution of Glu for Gly in the ectodomain of HER-3 (Accession #: NM_001982, nucleotide # 1877, and amino acid residue # 560).

Figure 4B shows high-affinity binding by Int8 RBD polypeptide to endogenous HER-3 on MCF7 breast cancer cells, independent of ligand activation.

Figure 4C shows binding of the Int8 RBD polypeptide to purified (wild-type) HER-3.

Figure 5A illustrates a binding curve showing that the Int8 RBD polypeptide bound to HER-2-transfected Cos-7 cells (K_D =50 ± 6nM; open squares) and to EGFR-transfected Cos-7 cells (K_D=78±10nM; filled squares) with binding affinities, assessed by comparative nonlinear regression analysis, that were not significantly different (P=0.40).

Figure 5B illustrates a binding curve showing that the Int8 RBD polypeptide bound to the IGF-IR/3T3 cells with an affinity (K_D =70±21) that was not significantly different (P=0.96) from the affinity for HER-2/3T3 cells (K_D=66± 16).

Figure 6A illustrates binding curves showing a direct comparison of the binding of herstatin to 3T3/HER-2 and 3T3/IGF-IR cells.

Figure 6B illustrates Cos-7 cell herstatin binding curves showing that the dissociation constant of herstatin for EGFR was similar to that of HER-2, and was unaffected by ligand occupation.

Figure 6C is a saturation binding curve showing that herstatin exhibited saturation binding to endogenous receptors in A431 epidermoid carcinoma cells, which express very high levels of EGFR and low levels of other ErbB receptors.

Figures 7A and 7B show that while herstatin blocked intracellular signaling (MAPK phosphorylation) by Heregulin (the ligand for HER-3 and HER-4) in MCF-7 cells (FIGURE 7A,

right-most two time series in upper panel), it does not affect FGF signaling (MAPK phosphorylation) in MCF-7 cells (FIGURE 7A, right-most two time series in lower panel), and did not inhibit IGF-1-mediated ERK phosphorylation in MCF-7 cells (FIGURE 7B).

Figure 7C shows that herstatin down-regulates HER-1, HER-3 and HER-4 receptors in MCF-7 cells.

Figure 7D shows that herstatin blocks EGF/EGFR-mediated intracellular signaling (MAPK phosphorylation) in MCF-7 cells.

Figure 8A and 8B show that herstatin inhibited IGF-1/IGF-1R-mediated activation of the PI3/Akt pathway that is important in cell survival. Figure 8A shows representative Western immunoblot showing IGF-I-induced Akt/PKB activation in MCF7 and MCF7/Hst cells. Figure 8B shows the graphical representation of 3 separate experiments, according to Figure 8A.

Figure 9 shows the effect of herstatin -expression on the expression levels of various signaling proteins. Herstatin expression in MCF7 breast carcinoma cells down-regulated IGF-1R, IRS-1, IRS-2 (also important in cell survival), and pKB/Akt expression, but MAPK expression was unaffected. Herstatin expression also induced expression of the p66 isoform of Shc, which is not detectable by Western Blot in parental MCF7 cells.

Figures 10A and 10B show the effect of herstatin on IGF-I-stimulated cell proliferation. Herstatin expression blocked IGF-1-mediated survival of MCF7 cells. Growth of parental MCF7 breast carcinoma cells and MCF7 cells stably transfected with herstatin, (A) low hst-expressing clone, and (B) high hst-expressing clone, was determined by the MTS assay as described under Example 1 herein. Cells were serum-starved for 24 hours and then treated with 5nM IGF-1 or vehicle, and growth was assessed at the indicated days.

DETAILED DESCRIPTION OF THE INVENTION

Herstatin is the only known alternative receptor product that functions as a ligand, and is the only mammalian secreted ligand that inhibits members (HER-2 and EGFR) of the EGF receptor family (see, *e.g.*, for background: Dougall et al., *Oncogene* 9:2109-23, 1994; Hynes & Stern, *Biochim Biophys Acta* 1198:165-84, 1994; and Tzahar & Yarden, *Biochim Biophys Acta* 1377:M25-37, 1998).

Aspects of the present invention describe and support HER-3, ΔEGFR, HER-4, and the IGF-IR as four additional (in addition to the previously disclosed binding to EGFR and HER-2) novel targets of herstatin and/or of its intron 8-encoded receptor binding domain (herein referred to as "Int8 RBD" or "RBD int8" polypeptide).

Additional aspects describe and support applicant's determination that intron 8 of the HER-2 gene, which is retained in an alternative HER-2 transcript (that encodes herstatin, encodes a 79-amino acid receptor binding domain (RBD) polypeptide (RBD Int8 polypeptide) that specifically binds to EGFR, HER-2, HER-3, ΔEGFR, HER-4, and the IGF-IR (RBD Int8 target receptors) with high affinity (*e.g.*, nM affinity), but not to a mutant form of HER-3 having a substitution of Glu for Gly in the ectodomain of HER-3 at residue number 560, nor to the FGFR-3.

In particular aspects, as disclosed herein, herstatin inhibits target receptor-mediated activation of the intracellular signaling pathways (*e.g.*, PI3/Akt, IRS-2, etc., pathways) that are important in cell survival, and further inhibit target receptor-mediated survival of cancer cells. Therefore, herstatin and/or RBD Int8 polypeptides and herstatin-, and/or RBD Int8 polypeptide-based agents (*e.g.*, conjugates with toxins, radionuclides, etc.) have utility as therapeutic agents for treatment of diseases or conditions (*e.g.*, cancer) characterized by cellular expression, or over-expression of a target receptor (*e.g.*, of EGFR, HER-2, HER-3, ΔEGFR, HER-4, and/or the IGF-IR).

According to additional aspects, while the intron 8-encoded domain was demonstrated herein to be critical for receptor binding, it did not affect target receptor activity indicating that the N-terminal subdomains I and II of herstatin are likely required for receptor inhibition.

Furthermore, as disclosed herein, while the intron 8-encoded RBD appears to be critical for the receptor binding activity of herstatin, it is not conserved between humans and rats, despite a high degree of sequence identify between the HER-2 receptor and its rat ortholog, neu. Consistent with this result, there are distinct regions in the ectodomains of these two receptors that have very little identity (Stein and Staros, 2000).

According to particular aspects, therefore, the HER-3, HER-4 and ΔEGF receptors are specific targets of herstatin and/or the RBD Int8 polypeptide, likely based on specific binding of

the RBD Int8-encoded domain. Moreover, and as in the case of the structurally related EGFR and HER-2 receptors, herstatin binds to and blocks the dimerization of the HER-3, HER-4 and ΔEGF receptors. As shown herein, for example, herstatin inhibits HER-4-mediated activation of the PI3/Akt pathway important in cells survival.

HER-3 is unique in the erbB family in that it is kinase-deficient, requiring an active receptor partner to signal. Additional aspects provide a mutant form of HER-3 that shows a lack of herstatin and/or RBD Int8 polypeptide binding. This mutant or variant form, therefore, has utility according to particular aspects of the present invention, for identification and/or screening of cells that are, at least to some extent, non-responsive, or at least less responsive to herstatin and/or RBD Int8 polypeptides, compared to cells expressing HER-3 forms that do bind herstatin and/or RBD Int8 polypeptides.

Surprisingly, according to particular aspects of the present invention, the IGF-1 receptor (IGF-1R) is also a specific target of herstatin and/or the RBD Int8 polypeptide, based on specific binding of the RBD Int8-encoded domain. The binding of herstatin and/or the RBD Int8 polypeptide to the IGF-IR with high affinity (*e.g.*, nM affinity) was entirely unexpected, because receptor ligands do not typically cross-react with receptors from different families. Consistent with this result, however, the IGF-IR appears to have regions of ectodomain sequence homology with the EGFR, and it is known that "crosstalk" occurs between the families, most notably, 'transactivation' of the EGFR by IGF-1 (Ahmed T, Farnie N, et al., 2004; and references therein). Therefore, herstatin and/or RBD Int8 polypeptides and herstatin-, and/or RBD Int8 polypeptide-based agents (*e.g.*, conjugates with toxins, radionuclides, etc.) have utility as therapeutic agents for treatment of diseases or conditions (*e.g.*, cancer) characterized by cellular expression, or over-expression of the IGF-IR.

In particular determinations, the binding affinity of herstatin, but not of the RBD Int8 polypeptide, was found to be somewhat weaker for IGF-IR than for HER-2 or the EGFR, indicating less stabilizing interaction between the N-terminus of herstatin and the IGF-1 receptor ectodomain relative to the corresponding EGFR ectodomain regions (the IGF-IR does not have a homologous dimerization loop (Garrett et al., *Cell* 110:763-73, 2002).

According to additional aspects of the present invention, herstatin, the RBD Int8

polypeptide and herstatin- and/or RBD Int8 polypeptide-based agents can be used to target EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR, and/or modulate signaling mediated by these target receptors.

DEFINITIONS

"Herstatin" refers to the polypeptides of SEQ ID NO:2, and additionally includes functional (*e.g.*, target receptor-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof.

"RBD Int8 polypeptide" refers to the polypeptides of SEQ ID NO:1, and additionally includes functional (*e.g.*, target receptor-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof.

"Mutant RBD Int8 polypeptide" or "mutant Int8 RBD polypeptide" refers to the intron 8-encoded receptor binding domain variants (with an Arg to Ile mutation at residue 31 thereof) of SEQ ID NO:3), and additionally includes functional (*e.g.*, target receptor non-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof. Representative, corresponding herstatin variants (Arg to Ile mutation at residue 371) are given as SEQ ID NO:4.

Functional herstatin, functional herstatin variants, functional Int8 RBD polypeptides, and functional Int8 RBD polypeptide variants are those proteins that display one or more of the biological activities of herstatin, including but not limited to target receptor binding, inhibition of receptor dimerization, modulation of receptor-mediated signal transduction, modulation of receptor activation, receptor down-regulation, etc. Particular aspects provide Functional herstatin, functional herstatin variants, functional Int8 RBD polypeptides, and functional Int8 RBD polypeptide variants having various binding affinities, including but not limited to those having a K_D of at least 20 nM, at least 40 nM, at least 60 nM, at least 80 nM, at least 100 nM, at least 120 nM, at least 140 nM, at least 160 nM, or at least 180 nM.

"EGFR," "HER-1" or "erbB-1" refer to the art-recognized human epidermal growth factor receptor, erbB-1 (cDNA: NM_005228, SEQ ID NO:5; protein: NP_005219, SEQ ID NO:6), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

"ΔEGFR" refers to the art-recognized receptor, ΔEGFR (cDNA: SEQ ID NO:7; protein: SEQ ID NO:8) (*see* Ekstrand et al., *PNAS* 89:4309-4313, 1992; and Nishikawa et al., *PNAS*

91:7727-7731, 1994) (comprising a deletion in the ECD; cDNA positions 275 through 1075, corresponding to exons 2-7 of the EGFR gene), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

"HER-2" or "erbB-2" refers to the art-recognized human receptor, erbB-2 (cDNA: NM_004448, SEQ ID NO:9; protein: NP_004439, SEQ ID NO:10), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

"HER-3" or "erbB-3" refers to the art-recognized human receptor, erbB-3 (cDNA: NM_001982, SEQ ID NO:11; protein: NP_001973, SEQ ID NO:12), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

The phrase "mutant form of HER-3" refers to a HER-3 protein having a substitution of Glu for Gly in the ectodomain of HER-3 corresponding to a single point mutation at nucleotide position 1877 ("a" instead of "g" at this position), resulting in substitution of Glu instead of Gly at residue position 560) (cDNA: SEQ ID NO:13; protein: SEQ ID NO:14).

"HER-4" or "erbB-4" refers to the art-recognized human receptor, erbB-4 (cDNA: NM_005235, SEQ ID NO:15; protein: NP_005226, SEQ ID NO:16), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

"IGF-1R" refers to the art recognized insulin-like growth factor 1 receptor (cDNA: NM_000875, SEQ ID NO:17; protein: NP_000866, SEQ ID NO:18), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

As used herein, a pharmaceutical effect refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

As used herein therapeutic effect means an effect resulting from treatment of a subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

As used herein, the term "subject" refers to animals, including mammals, such as human beings. As used herein, a patient refers to a human subject.

As used herein, the phrase "associated with" refers to certain biological aspects such as expression of a receptor or signaling by a receptor that occurs in the context of a disease or condition. Such biological aspect may or may not be causative or integral to the disease or condition but merely an aspect of the disease or condition.

As used herein, a biological activity refers to a function of a polypeptide including but not limited to complexation, dimerization, multimerization, receptor-associated kinase activity, receptor-associated protease activity, phosphorylation, dephosphorylation, autophosphorylation, ability to form complexes with other molecules, ligand binding, catalytic or enzymatic activity, activation including auto-activation and activation of other polypeptides, inhibition or modulation of another molecule's function, stimulation or inhibition of signal transduction and/or cellular responses such as cell proliferation, migration, differentiation, and growth, degradation, membrane localization, membrane binding, and oncogenesis. A biological activity can be assessed by assays described herein and by any suitable assays known to those of skill in the art, including, but not limited to *in vitro* assays, including cell-based assays, *in vivo* assays, including assays in animal models for particular diseases.

TABLE 1. Summary of SEQ ID NOS and accession numbers:

MOLECULE	cDNA	PROTEIN
RBD Int8 polypeptide(s))		SEQ ID NO:1
Herstatin (s)		SEQ ID NO:2
Mutant Int8 RBD polypeptide(s)		SEQ ID NO:3
Mutant Herstatin (s)		SEQ ID NO:4
EGFR (HER-1 or erbB-1)	SEQ ID NO:5 (NM_005228)	SEQ ID NO:6 (NP_005219)
ΔEGFR	SEQ ID NO:7	SEQ ID NO:8
HER-2 (erbB-2)	SEQ ID NO:9 (NM_004448)	SEQ ID NO:10 (NP_004439)
HER-3 (erbB-3)	SEQ ID NO:11 (NM_001982)	SEQ ID NO:12 (NP_001973)
Mutant form of HER-3	SEQ ID NO:13	SEQ ID NO:14

MOLECULE	cDNA	PROTEIN
HER-4 (erbB-4)	SEQ ID NO:15 (NM_005235)	SEQ ID NO:16 (NP_005226)
IGF-1R	SEQ ID NO:17 (NM_000875)	SEQ ID NO:18 (NP_000866)

Herstatin and/or RBD Int8 polypeptides and therapeutic agents

In preferred aspects, the present invention provides for the use of herstatin (SEQ ID NO:2), and variants and polypeptides thereof that bind to a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR). Also provided are uses of RBD Int8 polypeptides (SEQ ID NO:2), and receptor-binding variants and polypeptides thereof that bind to a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR).

Preferably, the herstatin, or variant thereof comprises an amino acid sequence of SEQ ID NO:2 (or of SEQ ID NO:2 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions), or a fragment of a sequence of SEQ ID NO:2 (or of SEQ ID NO:2 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions) of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, and wherein the polypeptide binds to the extracellular domain (ECD) of a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR) with an affinity binding constant of at least 10^7 M^{-1}, at least 5 x 10^7 M^{-1}, or at least 10^8 M^{-1}. Preferably, the herstatin, or variant thereof, is from about 350 to 419 contiguous residues in length. Preferably, the herstatin, or variant thereof, binds to the extracellular domain (ECD) of a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR) with an affinity binding constant of at least 10^7 M^{-1}, at least 5 x 10^7 M^{-1}, or at least 10^8 M^{-1}. Preferably, herstatin, or variant thereof, comprises a sequence of SEQ ID NO:2, or a conservative amino acid substitution variant thereof.

Preferably, the RBD Int8 polypeptides, and variants thereof, comprise an amino acid sequence of SEQ ID NO:1 (or of SEQ ID NO:1 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions), or a fragment of a sequence of SEQ ID NO:1 (or of SEQ ID NO:1 having from 1, to about 3, to about 5, to about 10, or to about 20

conservative amino acid substitutions) of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the extracellular domain (ECD) of a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR) with an affinity binding constant of about 10^7 M^{-1}, about 5×10^7 M^{-1}, about 10^8 M^{-1}, or greater (or at least 10^7 M^{-1}, at least 5×10^7 M^{-1}, or at least 10^8 M^{-1}). Preferably, the RBD Int8 polypeptide, or variant thereof is from about 69 to 79 contiguous residues in length with a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR) affinity binding constant of about 10^7 M^{-1}, about 5×10^7 M^{-1}, about 10^8 M^{-1}, or greater (or at least 10^7 M^{-1}, at least 5×10^7 M^{-1}, or at least 10^8 M^{-1}). Preferably, the RBD Int8 polypeptide, or variant thereof comprises a sequence of SEQ ID NO:1, or a conservative amino acid substitution variant thereof.

Specific Exemplary Embodiments:

Methods of treatment using a herstatin, or a variant thereof

A preferred embodiment of the present invention provides a method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of a herstatin, or of a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

In particular embodiments, the condition is a cellular proliferative condition or disorder, and preferably, the cellular proliferative condition or disorder is cancer.

In other embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length. Preferably, the herstatin, or variant thereof comprises the C-terminal 79 contiguous amino acids of SEQ ID NO:2, and binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

Further embodiment provide for application of the methods in instances where the cancer

is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different than herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants.

Additional embodiments further comprise administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell. Preferably, the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1. In particular embodiments, the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5 (HERCEPTIN™). In alternate embodiments, the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the herstatin, or the variant thereof. Preferably, the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

Yet further embodiments comprise administration of a therapeutically effective amount of a chemotherapeutic agent. In particular embodiments, the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramide, triethylenethiophosphoramide, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedepa, uredepa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

In preferred embodiments, the herstatin, or variant thereof, comprises SEQ ID NO:23, which corresponds to the most common herstatin sequence (wild-type).

Methods of treatment using an Int8 RBD polypeptide, or a variant thereof

Alternate preferred embodiments provide a method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of an Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

In particular embodiments, the condition is a cellular proliferative condition or disorder, and preferably the cellular proliferative condition or disorder is cancer.

In additional embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length. Preferably, the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

Further embodiments provide for application of the methods where the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different than herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants. Preferably, the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

Additional embodiments further comprise administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell. In particular embodiments, the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1. In a particular embodiment, the

receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5 (HERCEPTIN™). In alternate embodiments, the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the Int8 RBD polypeptide, or the variant thereof.

Yet additional embodiments further comprise administration of a therapeutically effective amount of a chemotherapeutic agent, and in particular embodiments, the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramide, triethylenethiophosphoramide, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedepa, uredepa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

In preferred embodiments, the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24, which corresponds to the most common Int8 RBD polypeptide sequence (wild-type).

Methods of cellular targeting

Yet further embodiments provide a method for targeting a therapeutic agent to target cells, comprising attaching the therapeutic agent to herstatin, or to a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

In particular embodiments, the target cell is a cancer cell.

In other embodiments the target cell optionally further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the herstatin, or variant thereof, comprises a polypeptide

selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length. Preferably, the herstatin, or variant thereof comprises the C-terminal 79 contiguous amino acids of SEQ ID NO:2, and binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

Alternate embodiments provide a method for targeting a therapeutic agent to target cells, comprising attaching the therapeutic agent to an Int8 RBD polypeptide, or to a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

In particular embodiments, the target cell is a cancer cell.

In other embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length. Preferably, the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

Pharmaceutical compositions

Yet additional embodiments provide pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, an agent selected from the group consisting of: (a) herstatin, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1; (b) a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1; (c) a receptor-specific antibody that binds to the extracellular domain (ECD) of a cellular receptor of the target cell;

and (d) combinations thereof, with the proviso that where the composition comprises the target cell receptor-specific antibody it also comprises at least one of the agents of (a) or (b).

Additional embodiments provide for a pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a first agent selected from the group consisting of: herstatin, or a variant thereof; a Int8 RBD polypeptide, or a variant thereof; and combinations thereof, the composition further comprising a second agent selected from the group consisting of: a receptor-specific antibody that binds to the extracellular domain (ECD) of a cellular receptor of the target cell; a small molecule receptor tyrosine kinase inhibitor; and combinations thereof, with the proviso that the receptor-specific antibody is not a HER-1 or HER-2-specific antibody.

Preferably, the herstatin, or variant thereof, comprises SEQ ID NO:23. Preferably, the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

In particular embodiments, the condition treated with the composition is a cellular proliferative condition or disorder, and preferably the cellular proliferative condition or disorder is cancer.

In additional embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, when agent (c) is present, the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the other agents (a) or (b).

In preferred embodiments agent (a) the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, and agent (b) the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

Further embodiments provide for a pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a polynucleotide that encodes a

herstatin, or a herstatin variant.

Yet further embodiments provide for a pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a polynucleotide that encodes an int8 RBD polypeptide, or an int8 RBD polypeptide variant.

Mutant/variant HER-3 screening assays

Particular embodiments provide for a method for identification of cells having HER-3 receptors that do not bind herstatin, int 8 RDB polypeptides, or variants thereof, comprising: obtaining a cellular sample; and determining, using one or more suitable assays, whether the cells express SEQ ID NO:14.

Additional embodiments provide for screening for cells that are, at least to some extent, non-responsive to herstatin, int 8 RDB polypeptides, or variants thereof, comprising obtaining a cellular sample; and determining, using one or more suitable assays, wherein the cells are determined to be at least to some extent, non-responsive to herstatin, int 8 RDB polypeptes, or variants thereof, express SEQ ID NO:14, wherein if the cells express SEQ ID NO:14.

Biologically Active Variants

Functional herstatin, functional herstatin variants, functional Int8 RBD polypeptides, and functional Int8 RBD polypeptide variants are those proteins that display one or more of the biological activities of herstatin, including but not limited to target receptor binding, inhibition of receptor dimerization, modulation of receptor-mediated signal transduction, modulation of receptor activation, receptor down-regulation, etc.

Variants of herstatin and/or RBD Int8 polypeptide have utility for aspects of the present invention. Variants can be naturally or non-naturally occurring. Naturally occurring variants (*e.g.*, polymorphisms) are found in humans or other species and comprise amino acid sequences which are substantially identical to the amino acid sequence shown in SEQ ID NO:1 or 2. Species homologs of the protein can be obtained using subgenomic polynucleotides of the invention, as described below, to make suitable probes or primers for screening cDNA

expression libraries from other species, such as mice, monkeys, yeast, or bacteria, identifying cDNAs which encode homologs of the protein, and expressing the cDNAs as is known in the art.

Non-naturally occurring variants which retain substantially the same biological activities as naturally occurring protein variants, specifically the target RBD activity and the modulation of target receptor signaling activity, are also included here. Preferably, naturally or non-naturally occurring variants have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequence shown in SEQ ID NOS:1 or 2. More preferably, the molecules are at least 98% or 99% identical. Percent identity is determined using any method known in the art. A non-limiting example is the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1. The Smith-Waterman homology search algorithm is taught in Smith and Waterman, *Adv. Appl. Math.* 2:482-489, 1981.

As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are generally in the "L" isomeric form. Residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property is retained by the polypeptide. NH2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in J. Biol. Chem., 243:3552-59 (1969) and adopted at 37 C.F.R. §§ 1.821 - 1.822, abbreviations for amino acid residues are shown in Table 2:

TABLE 2 – Table of Correspondence

SYMBOL		
1-Letter	**3-Letter**	**AMINO ACID**
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine

SYMBOL		
1-Letter	**3-Letter**	**AMINO ACID**
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	Praline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	aspartic acid
N	Asn	Asparagines
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

It should be noted that all amino acid residue sequences represented herein by a formula have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase "amino acid residue" is defined to include the amino acids listed in the Table of Correspondence and modified and unusual amino acids, such as those referred to in 37 C.F.R. §§ 1.821-1.822, and incorporated herein by reference. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues or to an amino-terminal group such as NH_2 or to a carboxyl-terminal group such as COOH.

Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity can be found using computer

programs well known in the art, such as DNASTAR software. Preferably, amino acid changes in the protein variants disclosed herein are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting variant.

Variants of the herstatin and/or RBD Int8 polypeptide disclosed herein include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (*e.g.*, pegylated molecules). Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art. Variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the proteins are also variants.

A subset of mutants, called muteins, is a group of polypeptides in which neutral amino acids, such as serines, are substituted for cysteine residues which do not participate in disulfide bonds. These mutants may be stable over a broader temperature range than native secreted proteins (see, *e.g.*, Mark *et al.*, United States Patent No. 4,959,314).

Preferably, amino acid changes in the herstatin and/or RBD Int8 polypeptide variants are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar

(alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting secreted protein or polypeptide variant. Properties and functions of herstatin and/or RBD Int8 polypeptide protein or polypeptide variants are of the same type as a protein comprising the amino acid sequence encoded by the nucleotide sequence shown in SEQ ID NO:1 or 2, although the properties and functions of variants can differ in degree.

Herstatin and/or RBD Int8 polypeptide variants include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (*e.g.*, pegylated molecules). Herstatin and/or RBD Int8 polypeptide variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the proteins are also variants. Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art.

It will be recognized in the art that some amino acid sequences of the herstatin and/or RBD Int8 polypeptides of the invention can be varied without significant effect on the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there are critical areas on the protein which determine activity. In general, it is possible to replace residues that form the tertiary structure, provided that residues performing a similar function are used. In other instances, the type of residue may be completely unimportant if the alteration occurs at a non-critical region of the protein. The replacement of amino acids can also change the selectivity of binding to cell surface receptors (Ostade et al., *Nature 361*:266-268, 1993). Thus, the herstatin and/or RBD Int8 polypeptides of the present invention may include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the disclosed protein. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic (see, *e.g.*, Pinckard et al., *Clin. Exp. Immunol. 2*:331-340 (1967); Robbins et al., *Diabetes 36*:838-845 (1987); and Cleland et al., *Crit. Rev. Therapeutic Drug Carrier Systems 10*:307-377 (1993)).

Amino acids in the herstatin and/or RBD Int8 polypeptides of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science 244*:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as binding to a natural or synthetic binding partner. Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol. 224*:899-904 (1992) and de Vos et al. *Science 255*:306-312 (1992)).

As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein. Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of substitutions for any given herstatin and/or RBD Int8 polypeptide will not be more than 50, 40, 30, 25, 20, 15, 10, 5 or 3.

In addition, pegylation of herstatin and/or RBD Int8 polypeptides and/or muteins is expected to provide such improved properties as increased half-life, solubility, and protease resistance. Pegylation is well known in the art.

Fusion Proteins

Fusion proteins comprising proteins or polypeptide fragments of herstatin and/or RBD Int8 polypeptide can also be constructed. Fusion proteins are useful for generating antibodies

against amino acid sequences and for use in various targeting and assay systems. For example, fusion proteins can be used to identify proteins which interact with a herstatin and/or RBD Int8 polypeptide of the invention or which interfere with its biological function. Physical methods, such as protein affinity chromatography, or library-based assays for protein-protein interactions, such as the yeast two-hybrid or phage display systems, can also be used for this purpose. Such methods are well known in the art and can also be used as drug screens. Fusion proteins comprising a signal sequence can be used.

A fusion protein comprises two protein segments fused together by means of a peptide bond. Amino acid sequences for use in fusion proteins of the invention can be utilize the amino acid sequence shown in SEQ ID NO:1 or 2 or can be prepared from biologically active variants of SEQ ID NO:1 or 2, such as those described above. The first protein segment can include of a full-length herstatin and/or RBD Int8 polypeptide.

Other first protein segments can consist of about 50 to about 79 contiguous amino acids from SEQ ID NO:1, or, with respect to SEQ ID NO:2, from about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids of SEQ ID NO:2 are present, or from about 350 to 419 contiguous residues in length wherein the C-terminal 79 contiguous amino acids of SEQ ID NO:2 are present.

The second protein segment can be a full-length protein or a polypeptide fragment. Proteins commonly used in fusion protein construction include β-galactosidase, β-glucuronidase, green fluorescent protein (GFP), autofluorescent proteins, including blue fluorescent protein (BFP), glutathione-S-transferase (GST), luciferase, horseradish peroxidase (HRP), and chloramphenicol acetyltransferase (CAT). Additionally, epitope tags can be used in fusion protein constructions, including histidine (His) tags, FLAG tags, influenza hemagglutinin (HA) tags, Myc tags, VSV-G tags, and thioredoxin (Trx) tags. Other fusion constructions can include maltose binding protein (MBP), S-tag, Lex a DNA binding domain (DBD) fusions, GAL4 DNA binding domain fusions, and herpes simplex virus (HSV) BP16 protein fusions.

These fusions can be made, for example, by covalently linking two protein segments or by standard procedures in the art of molecular biology. Recombinant DNA methods can be used to prepare fusion proteins, for example, by making a DNA construct which comprises a coding

region for the protein sequence of SEQ ID NO:1 or 2 in proper reading frame with a nucleotide encoding the second protein segment and expressing the DNA construct in a host cell, as is known in the art. Many kits for constructing fusion proteins are available from companies that supply research labs with tools for experiments, including, for example, Promega Corporation (Madison, WI), Stratagene (La Jolla, CA), Clontech (Mountain View, CA), Santa Cruz Biotechnology (Santa Cruz, CA), MBL International Corporation (MIC; Watertown, MA), and Quantum Biotechnologies (Montreal, Canada; 1-888-DNA-KITS).

Cell Targeting

According to particular aspects of the present invention, herstatin- and/or RBD Int8 polypeptide-based agents can be used to target EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R on cells (*e.g.*, cancer cells). Herstatin- and/or RBD Int8 polypeptide-based agents can be used to deliver a locally acting biological agent that will affect the targeted cell.

Each of the target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R) is expressed on the surface of cells and are accessible to exogenous molecules. Where any of these target receptors are present at higher levels on cancer cells as compared to non-cancer cells, they can be utilized as preferential targets for systemic herstatin- and/or RBD Int8 polypeptide-based agents -based therapies. The differential expression of these target receptors enables the specificity of herstatin- and/or RBD Int8 polypeptide-based agents-based therapy. Herstatin- and/or RBD Int8 polypeptide-based cytotoxic agents directed against the target receptor preferentially affect cancer cells over normal tissue. For example, an herstatin- or RBD Int8 polypeptide-radioisotope conjugate that binds a target receptor (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R) present predominantly on cancer cells would be expected to selectively affect those cells within a treated individual. Preferably, the target is accessible to the herstatin- and/or RBD Int8 polypeptide-based agent, and is found in substantially greater concentrations on the targeted cancer cells than non-cancer cells.

Therefore, the present invention includes™- and/or RBD Int8 polypeptide-based agents

specific to one or more of the target receptors that will enable or facilitate treatment of cancer.

In particular aspects, herstatin- and/or RBD Int8 polypeptides are conjugated or coupled to toxins.

In alternate embodiments, herstatin- and/or RBD Int8 polypeptides are conjugated or coupled to radionuclides.

Additional embodiments provide for herstatin- and/or RBD Int8 polypeptide-coated liposomes which contain one or more biologically active compounds.

In particular aspects, binding of an herstatin- and/or RBD Int8 polypeptide-agent to a cell is sufficient to inhibit growth (*e.g.*, cytostatic effects) or kill the target cell (cytotoxic effects). The mechanism of these activities may vary, but may involve herstatin- and/or RBD Int8 polypeptide-dependent cell-mediated cytotoxicity, activation of apoptosis, inhibition of ligand-receptor function, or provide a signal for complement fixation. In fact, herstatin- and/or RBD Int8 polypeptide-agents may exhibit one or several of such activities. In particular aspects, herstatin- and/or RBD Int8 polypeptide-agents are cytostatic, but not cytotoxic. Preferably, herstatin and/or RBD Int8 polypeptide-agents bind to target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R), and are either cytoxic or cytostatic.

In particular embodiments, herstatin- and/or RBD Int8 polypeptide-agents can are conjugated or coupled to a diverse array of compounds which include, but are not limited to proteins, toxins or cytotoxic agents, radionuclides, apoptotic factors), anti-angiogenic compounds or other biologically active compounds which will inhibit the growth of or kill the target cell or tissue. For example, cytotoxic or cytostatic agents include, but are not limited to, diphtheria toxin and Pseudomonas exotoxin, ricin, gelonin, doxorubicin and its derivatives, iodine-131, yttrium-90, indium-111, RNAse, calicheamicin, apoptotic agents, and antiangiogenic agents. According to aspects of the present invention, herstatin- and/or RBD Int8 polypeptides coupled to these compounds are used to adversely affect cells displaying one or more target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R).

Toxins can also be targeted to specific cells by incorporation of the toxin into herstatin-

and/or RBD Int8 polypeptide-coated liposomes. The herstatin- and/or RBD Int8 polypeptide-based agent directs the liposome to the target cell where the bioactive compound is released. For example, cytotoxins in herstatin- and/or RBD Int8 polypeptide-coated liposomes are used to treat cancer. In alternate embodiments, these targeted liposomes are loaded with DNA encoding bioactive polypeptides (*e.g.*, inducible nitric oxide synthase).

Prodrugs or enzymes can also be delivered to targeted cells by specific herstatin- and/or RBD Int8 polypeptide-agents. In this case the herstatin conjugate consists of an herstatin- and/or RBD Int8 polypeptide-based agent coupled to a drug that can be activated once the antibody binds the target cell. Examples of this strategy using antibodies have been reviewed (*e.g.*, Denny 2001; and Xu and McLeod 2001).

Therefore, in particular embodiments, herstatin- and/or RBD Int8 polypeptide-prodrug/enzyme conjugates targeted to one or more target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R) have utility for the treatment of cancer.

The specificity and high affinity of the herstatin- and/or RBD Int8 polypeptide-based agents makes them ideal candidates for delivery of toxic agents to a specific subset of cellular targets. Preferably, one or more target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R) are present at higher levels on the target cells (*e.g.*, cancer, tumor cells) than on non-cancer cells.

Pharmaceutical Compositions and Therapeutic Uses

Pharmaceutical compositions of the invention can comprise herstatin and/or RBD Int8 polypeptides, or herstatin- and/or RBD Int8 polypeptide-based agents of the claimed invention in a therapeutically effective amount. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition, and the therapeutics or

combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance. However, the effective amount for a given situation is determined by routine experimentation and is within the judgment of the clinician. For purposes of the present invention, an effective dose will generally be from about 0.01 mg/ kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the herstatin and/or RBD Int8 polypeptide constructs in the individual to which it is administered. A non-limiting example of a pharmaceutical composition is a composition that either enhances or diminishes signaling mediated by the inventive target receptors (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR). Where such signaling promotes a disease-related process, modulation of the signaling would be the goal of the therapy.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which can be administered without undue toxicity. Suitable carriers can be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Pharmaceutically acceptable carriers in therapeutic compositions can include liquids such as water, saline, glycerol and ethanol. Auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, can also be present in such vehicles. Typically, the therapeutic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. Liposomes are included within the definition of a pharmaceutically acceptable carrier. Pharmaceutically acceptable salts can also be present in the pharmaceutical composition, *e.g.*, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., New Jersey,

1991).

Delivery Methods. Once formulated, the compositions of the invention can be administered directly to the subject or delivered *ex vivo*, to cells derived from the subject (*e.g.*, as in *ex vivo* gene therapy). Direct delivery of the compositions will generally be accomplished by parenteral injection, *e.g.*, subcutaneously, intraperitoneally, intravenously or intramuscularly, myocardial, intratumoral, peritumoral, or to the interstitial space of a tissue. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal applications, needles, and gene guns or hyposprays. Dosage treatment can be a single dose schedule or a multiple dose schedule.

Methods for the *ex vivo* delivery and reimplantation of transformed cells into a subject are known in the art and described in *e.g.*, International Publication No. WO 93/14778. Examples of cells useful in *ex vivo* applications include, for example, stem cells, particularly hematopoetic, lymph cells, macrophages, dendritic cells, or tumor cells. Generally, delivery of nucleic acids for both *ex vivo* and *in vitro* applications can be accomplished by, for example, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, direct microinjection of the DNA into nuclei, and viral-mediated, such as adenovirus or alphavirus, all well known in the art.

In a preferred embodiment, disorders of proliferation, such as cancer, can be amenable to treatment by administration of a therapeutic agent based on the provided polynucleotide or corresponding polypeptide. The therapeutic agent can be administered in conjunction with one or more other agents including, but not limited to, receptor-specific antibodies and/or chemotherapeutic (*e.g.*, anti-neoplastic agents). Administered "in conjunction" includes administration at the same time, or within 1 day, 12 hours, 6 hours, one hour, or less than one hour, as the other therapeutic agent(s). The compositions may be mixed for co-administration, or may be administered separately by the same or different routes.

The dose and the means of administration of the inventive pharmaceutical compositions are determined based on the specific qualities of the therapeutic composition, the condition, age, and weight of the patient, the progression of the disease, and other relevant factors. For

example, administration of polynucleotide therapeutic compositions agents of the invention includes local or systemic administration, including injection, oral administration, particle gun or catheterized administration, and topical administration. The therapeutic polynucleotide composition can contain an expression construct comprising a promoter operably linked to a polynucleotide encoding, for example, SEQ ID NO:2, or encoding about 80 to 419 (or about 350 to 419) contiguous amino acids of SEQ ID NO:2. Various methods can be used to administer the therapeutic composition directly to a specific site in the body. For example, a small metastatic lesion is located and the therapeutic composition injected several times in several different locations within the body of tumor. Alternatively, arteries which serve a tumor are identified, and the therapeutic composition injected into such an artery, in order to deliver the composition directly into the tumor. A tumor that has a necrotic center is aspirated and the composition injected directly into the now empty center of the tumor. X-ray imaging is used to assist in certain of the above delivery methods.

Herstatin and/or RBD Int8 polypeptide-mediated targeted delivery of therapeutic agents to specific tissues can also be used. Receptor-mediated DNA delivery techniques are described in, for example, Findeis et al., *Trends Biotechnol.* (1993) *11*:202; Chiou et al., *Gene Therapeutics: Methods And Applications Of Direct Gene Transfer* (J.A. Wolff, ed.) (1994); Wu et al., *J. Biol. Chem.* (1988) *263*:621; Wu et al., *J. Biol. Chem.* (1994) *269*:542; Zenke et al., *Proc. Natl. Acad. Sci.* (*USA*) (1990) *87*:3655; Wu et al., *J. Biol. Chem.* (1991) *266*:338. Therapeutic compositions containing a polynucleotide are administered in a range of about 100 ng to about 200 mg of DNA for local administration in a gene therapy protocol. Concentration ranges of about 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA can also be used during a gene therapy protocol. Factors such as method of action (*e.g.*, for enhancing or inhibiting levels of the encoded gene product) and efficacy of transformation and expression are considerations which will affect the dosage required for ultimate efficacy of the subgenomic polynucleotides. Where greater expression is desired over a larger area of tissue, larger amounts of subgenomic polynucleotides or the same amounts readministered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions of, for example, a tumor site, may

be required to effect a positive therapeutic outcome. In all cases, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.

The therapeutic polynucleotides and polypeptides of the present invention can be delivered using gene delivery vehicles. The gene delivery vehicle can be of viral or non-viral origin (see generally, Jolly, *Cancer Gene Therapy* (1994) *1*:51; Kimura, *Human Gene Therapy* (1994) *5*:845; Connelly, *Human Gene Therapy* (1995) *1*:185; and Kaplitt, *Nature Genetics* (1994) *6*:148). Expression of such coding sequences can be induced using endogenous mammalian or heterologous promoters. Expression of the coding sequence can be either constitutive or regulated.

Viral-based vectors for delivery of a desired polynucleotide and expression in a desired cell are well known in the art. Exemplary viral-based vehicles include, but are not limited to, recombinant retroviruses (see, *e.g.*, WO 90/07936; WO 94/03622; WO 93/25698; WO 93/25234; U.S. Patent No. 5, 219,740; WO 93/11230; WO 93/10218; U.S. Patent No. 4,777,127; GB Patent No. 2,200,651; EP 0 345 242; and WO 91/02805), alphavirus-based vectors (*e.g.*, Sindbis virus vectors, Semliki forest virus (ATCC VR-67; ATCC VR-1247), Ross River virus (ATCC VR-373; ATCC VR-1246) and Venezuelan equine encephalitis virus (ATCC VR-923; ATCC VR-1250; ATCC VR 1249; ATCC VR-532), and adeno-associated virus (AAV) vectors (see, *e.g.*, WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and WO 95/00655). Administration of DNA linked to killed adenovirus as described in Curiel, *Hum. Gene Ther.* (1992) *3*:147 can also be employed.

Non-viral delivery vehicles and methods can also be employed, including, but not limited to, polycationic condensed DNA linked or unlinked to killed adenovirus alone (see, *e.g.*, Curiel, *Hum. Gene Ther.* (1992) *3*:147); ligand-linked DNA (see, *e.g.*, Wu, *J. Biol. Chem.* *264*:16985 (1989)); eukaryotic cell delivery vehicles cells (see, *e.g.*, U.S. Patent No. 5,814,482; WO 95/07994; WO 96/17072; WO 95/30763; and WO 97/42338) and nucleic charge neutralization or fusion with cell membranes. Naked DNA can also be employed. Exemplary naked DNA introduction methods are described in WO 90/11092 and U.S. Patent No. 5,580,859. Liposomes that can act as gene delivery vehicles are described in U.S. Patent No. 5,422,120; WO 95/13796; WO 94/23697; WO 91/14445; and EP 0524968. Additional approaches are

described in Philip, *Mol. Cell Biol. 14*:2411 (1994), and in Woffendin, *Proc. Natl. Acad. Sci.* (1994) *91*:11581-11585.

Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in Woffendin et al., *Proc. Natl. Acad. Sci. USA 91*(24):11581 (1994). Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials or use of ionizing radiation (see, *e.g.*, U.S. Patent No. 5,206,152 and WO 92/11033). Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun (see, *e.g.*, U.S. Patent No. 5,149,655); use of ionizing radiation for activating transferred gene (see, *e.g.*, U.S. Patent No. 5,206,152 and WO 92/11033).

Exemplary Conditions Treatable and Combination Therapies

The present invention, for the first time, not only discloses that herstatin and/or the intron 8-encoded domain thereof (referred to herein as "int8 RBD"polypeptides), and variants thereof, not only bind with high affinity (*e.g.*, at nM concentrations) to: all four of the ErbB receptors EGFR (HER-1, erbB-1), HER-2 (erbB-2), HER-3 (erbB-3), and HER-4 (erbB-4), and to ΔEGFR and the IGF-1 receptor, but also discloses that such target receptor binding has novel and substantial utility to modulate intracellular signaling mediated by these receptors.

Therefore, the present invention encompasses a broad range of utilities, including therapeutic utilities. For example, particular embodiments provide novel methods and compositions for the treatment of cancer and other conditions and disorders characterized by target receptor expression or over-expression, and/or target receptor-mediated signaling or aberrant signaling.

Specific embodiments provide a method for treating cancer, comprising administering a therapeutically effective amount of herstatin, or of a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors. Alternatively, a therapeutically effective amount of a Int8 RBD polypeptide, or of a variant thereof, that binds to the extracellular domain of a target

receptor selected from the group consisting of: Δ EGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, is administered. The methods also encompass treatments where the cancer cells further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

Combination therapies are also encompassed by aspects of the present invention. For example, the inventive methods may further comprise administration of a therapeutically effective amount of: a receptor-specific antibody that binds to the extracellular domain of a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-1R. Alternatively, the inventive methods may further comprise administration of chemotherapeutic agents, such as antineoplastic agents. Examples of anti-neoplastic agents are cyclophosphamide, triethylenephosphoramide, triethylenethiophosphoramide, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedepa, uredepa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

Treatment of refractory cancer. By virtue of their activation of the PI3K and MAPK cascades and potentially other signal transduction pathways, both the EGF and IGF receptor families are major regulators of cell growth and survival, and dysregulation of either receptor family can lead to uncontrolled growth and tumorgenesis. Moreover, 'cross-talk' is believed to occur between these receptor families, and various studies support the concept that redundant signaling through IGF-IR maintains activation of critical pathways for survival in the presence of EGFR family inhibitors. Such cross-talk and redundant signaling has been shown to be involved in cancers that are, or that become refractory to treatment by, for example, a particular receptor-specific agent (*e.g.*, antibody reagent, or small molecule receptor tyrosine kinase inhibitor) or class of agents; that is, such cancers do not respond, respond only weakly, or

progressively become less responsive to particular agents, by virtue of intracellular signaling mediated by a receptor other than the one being targeted by the particular agent. These findings all point to the need to for a multi-functional inhibitor that simultaneously targets both the EGF and IGF-IR families. Aspects of the present invention have met this need.

Accordingly, further embodiments provide for application of the methods where the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different than herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants. Preferably, the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

According to the present invention therefore, herstatin or Int8 RBD polypeptides, and variants thereof can be used in therapeutic methods and pharmaceutical compositions to treat a variety of conditions having an aspect related to, or associated with altered target receptor expression, altered target receptor expression, target receptor-mediated signaling, or altered target receptor-mediated signaling at a cellular level. Such methods comprising administering to a subject having such a condition, a therapeutically effective amount of a herstatin or Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one cellular target receptor.

The present invention will now be illustrated by reference to the following examples which set forth particularly advantageous embodiments. However, it should be noted that these embodiments are illustrative and are not to be construed as restricting the invention in any way.

EXAMPLE 1

(Materials and Methods)

Cell lines, transfections, expression vectors, western blots and antibodies

Cell lines. The 3T3/HER-2 cells were previously described (Lin et al., *Mol. Cell. Endocrinol.*, 69:111-9, 1990). The 3T3/IGF-IR cells were from Dr. Charles Roberts, OHSU, Portland, OR. MCF7 breast carcinoma cells were obtained from the American Type Culture

Collection and maintained at 37°C/5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) and gentamicin (0.25 μg/ml). Media and supplements were purchased from Gibco BRL-Life Technologies (Grand Island, NY). Hst-expressing MCF7 clones (previously characterized in Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003), were maintained under the same conditions as parental MCF7 cells in media supplemented with 0.5 mg/ml G418 sulfate.

Transfections. For transient transfections, 2 μg of empty vector or 2 μg EGFR, HER-2, HER-3, HER-4, ΔEGFR, or FGFR-3-myc expression vectors were added with Lipofectamine™ (GIBCO-BRL) to Cos-7 cells in 6 cm plates.

Expression vectors. The HER-2 and EGFR expression plasmids were previously described (Azios et al., *Oncogene* 20:5199-209, 2001), ΔEGFR was a gift from Dr. Webster Cavenee (Ludwig Institute for Cancer Research, UCSD, La Jolla, California), the FGFR-3-myc construct was from Dr. William Horton (Shriners Research Hospital, Portland, OR), and the HER-4 expression plasmid was a gift of Dr. Nancy Hynes (Friedrich Miescher-Institute for Biomedial Research, Basel, Switzerland).

Antibodies. Antibodies against the β-subunit of IGF-IR were from Dr. Charles Roberts (Oregon Health & Science University). All primary antibodies were used at a 1:1000 dilution and incubated with Western blots overnight at 4°C, unless otherwise indicated. Polyclonal antibodies (IGF-IR and IRS-1) and monoclonal antibody PY20 were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Monoclonal ERK 1/2 and polyclonal pERK 1/2 and Akt/PKB antibodies were purchased from Cell Signaling Technologies (Boston, MA). Monoclonal herstatin and polyclonal IRS-2 antibodies were obtained from Upstate Biotechnology (Lake Placid, NY). Polyclonal pAkt/PKB and pIGF-IR antibodies were purchased from Biosource International (Hopkinton, MA) and polyclonal anti-Shc antibody was obtained from Transduction Labs (Lexington, KY).

Western blot analysis. To analyze receptors by Western blot analysis, proteins were resolved by SDS-PAGE and electro-transferred onto nitrocellulose membranes (BioRad, Hercules, CA). Blots were blocked in 5% milk and incubated with primary antibody overnight at 4°C. The antibodies included anti-HER-2 (Christianson et al., *Cancer Res.* 58:5123-9, 1998)

and anti-EGFR, anti-HER-3, anti-HER-4, which were all rabbit polyclonal antibodies against the receptor C-terminal domains (Santa Cruz Biotechnology). After washing, the blots were incubated with secondary antibody conjugated to HRP for 30 min (BioRad, Hercules, CA). The membranes were developed with SuperSignal™ West Dura (Pierce, Rockford, IL) and exposed to x-ray film. In particular studies, cells were grown to ~80% confluency, serum-starved overnight in DMEM, and treated with 14 nM EGF, 5 nM IGF-I, or 20 nM IGF-II (in some experiments) for the times indicated. For Western immunoblots, cells were washed twice with ice-cold 1x PBS and lysed in 1x SDS sample buffer (Maniatis) without DTT or dye and boiled for 5 min. After clarification by centrifugation at 13,000 rpm for 5 min., protein concentration was determined using a detergent-compatible protein assay kit (Bio-Rad; Hercules, CA). DTT was then added to 100 mM and bromophenol blue to 0.1% (w/v) and samples were boiled again for 5 min. 20 mg protein was run on a 10% SDS-PAGE and blotted onto nitrocellulose (Amersham Pharmacia Biotech; Piscataway, NJ). Blots were probed with a phospho-specific antibody, stripped in 5x stripping buffer (Maniatis) and reprobed with the respective pan antibody. For immunoprecipitation, cells were washed twice with ice-cold 1x PBS, lysed in NP-40 lysis buffer [1% NP-40, 150 mM NaCl, 10% glycerol, 20 mM Tris-HCl (pH 8.0), 1 mM EDTA (pH 8.0), 0.2% SDS, complete protease inhibitors (Roche Diagnostics; Indianapolis, IN), 1 mM $NaVO_4$, and 1 mg/ml pepstatin] and kept on ice for 30 min, inverting the tubes every 2 minutes. Lysates were then centrifuged at 13,000 rpm for 15 minutes and the supernatant transferred to a new tube. Protein concentration was determined as above. For IGF-IR, 1 mg of whole-cell lysate protein was immunoprecipitated with 16 mg of anti-IGF-IR antibody and incubated overnight at 4°C while rocking. For IRS-1 and IRS-2, 500 mg of whole-cell lysate protein was incubated overnight with 10 mg antibody. 100 ml of protein A-agarose bead slurry (Amersham Pharmacia Biotech) was added for 2 hours rocking at 4°C. Three washes were performed and the pellet was boiled in 2x SDS sample buffer (Maniatis). The beads were spun down and the supernatant loaded onto a 10% (IGF-IR) or 7% (IRS-1/2) SDS-PAGE and blotted as above. Blots were probed with PY20, stripped as above, and reprobed with their respective antibodies. Binding of primary antibodies was detected by enhanced chemiluminescence (Amersham), and film exposures were quantified using a scanning densitometer (Bio-Rad).

Sequencing of human, monkey and rat Intron 8 regions:

Human. Human genomic DNA was obtained from blood samples (supplied by Dr. David Henner, OHSU) from individuals 18 years or more, after giving informed consent, with approval by the Institutional Review Board of OHSU. The samples, assigned random four-digit numbers, could not be traced to patient identity. The polymerase chain reaction (PCR) was employed to amplify intron 8 using primers: 3' AACACAGCGGTGTGAGAAGTGC (exon 8) (SEQ ID NO:19) and 5' GTATCGGTAGTTCATTTCCTTTGGTTGC (intron 9) (SEQ ID NO:20). The reactions were cycled (95°C for 2 minutes, 95°C for 30 seconds, 69°C for 30 seconds, 72°C for 30 seconds) for 30 cycles. PCR products were purified and subjected to cycle-sequencing. Electropherograms were individually reviewed to detect polymorphic alleles. Samples found to contain a polymorphism were sequenced at least once more to confirm the mutation.

Monkey. Rhesus monkey DNA, provided by Dr. Scott Wong (ORPC, Portland, OR) was amplified and sequenced using the above primers.

Rat. Intron 8 in rat genomic DNA (provided by Dr. John Adelman, Vollum Institute, Portland, OR) was amplified by PCR using rat specific primers: 5'-CTA CCT GTC TAC GGA AGT GG-3' (SEQ ID NO:21) and 5'-TTC CGG GCA GAA ATG CCA GG-3' (SEQ ID NO:22). The cycling parameters were: 94°C, 30"; 62° C, 30"; 72°C, 60", for 25 cycles.

Expression and purification of intron 8-encoded peptide (Int8) and herstatin:

Receptor binding domain (RBD). Intron 8 cDNA was cloned into the pET 30 bacterial expression vector (Novagen , Madison, WI), expressed in bacteria (BL-21), and purified by nickel affinity chromatography as described (Doherty et al., *Supra*).

Herstatin. For purification of insect herstatin, S2 insect cells, stably transfected with 6xHis tagged-herstatin in the pMT/BiP expression plasmid (Invitrogen, Carlsbad, CA), were induced with 100 μM cupric sulfate for about 16hrs. Herstatin was purified to about 90% purity

by Ni-NTA (Qiagen, Valencia, CA) affinity chromatography as previously described (Jhabvala-Romero et al. *Supra.*).

Cell binding studies:

ELISA. Monolayer cultures of ~2 x 10^6 cells were plated in 6-well tissue culture plates, and were incubated with purified herstatin or int8 peptide for 2 hours at 4°C in serum-free DMEM. Cells were washed with Phosphate Buffered Saline (PBS) and extracted in 50mM Tris·HCl, pH 7.0, 1.0% NP-40. Int8 peptide or herstatin bound to cells were quantified using a sandwich herstatin ELISA per manufacturer's instructions (Upstate Biotechnology, Lake Placid, NY).

The dissociation constant (K_D) and maximal binding (B_{max}) of herstatin or the int8 peptide were determined by nonlinear regression analysis of the plot of pmol of bound *versus* nM of herstatin or int8 peptide added. Statistical comparisons between different binding curves were performed by extra sums-of-squares F-test nonlinear regression coefficients. All tests were performed ($\alpha = 0.05$) using GraphPad Prism 4™ software (GraphPad™ Software, 1994-2003).

Pull-down assays with int8 peptide immobilized on protein S agarose:

About 100 µl of a 50% suspension of S-protein agarose (Novagen) was incubated with or without 100 µg of int8 peptide with an S-protein tag, at room temperature for 1hr, and then washed twice with 500 µl PBS. The agarose samples were then incubated at room temperature for 1 hr with 200 µg of transfected Cos-7 cell extract, then was washed twice with 500 µl of PBS with 1% NP40. The proteins associated with the resin were eluted at 92°C for 2 min in 40µl of SDS-sample buffer, and analyzed as a Western blot.

Growth assays. Cells ($4 \cdot 10^4$) were plated in quadruplicate in 24-well plates, incubated in serum-free DMEM for 24 hours, and treated with either 5 nM IGF-I (GroPep; Adelaide,

Australia) or 10 mM HCl as vehicle. Following serum starvation, and for four subsequent days at 24-hour intervals, cell monolayers were washed with PBS and incubated for 30 minutes at 37°C with 30 µl of MTS reagent [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl-2H-tetrazolium) inner salt Aqueous One Solution (Promega; Madison, WI) dissolved in 270 ml PBS] per well. Absorbance readings were obtained at 490 nm in a Bio-Tek plate reader.

EGFR inhibitor studies

Control MCF7 cells were serum-starved overnight and treated with the EGFR kinase inhibitor AG1478 (conc. in DMSO) or vehicle for 5 min. prior to the addition of 14 nM EGF or 5 nM IGF-I. After 5 min. of growth factor treatment, cell lysates were prepared and analyzed for ERK and Akt/PKB activation as described above.

EXAMPLE 2

(Herstatin, and its intron-encoded receptor-binding domain, were shown to bind specifically to IGF-1R with high (*e.g.*, nm) binding affinity)

The interaction of the receptor binding domain (RBD, encoded by HER-2 intron 8; int8 peptide) of herstatin with IGF-1R in transfected 3T3 cells was investigated. According to particular embodiments of the present invention, both full-length herstatin and its RBD bind specifically to IGF-1R with high binding affinity (*e.g.*, nm), and IGF-IR was thus shown herein to be a target of herstatin.

Methods. Cell lines, expression vectors, protein purification, pull down assays, antibodies, Western blot analysis and ELISA assays were as described under EXAMPLE 1, herein above.

Results. Figure 1A demonstrates that the Int8 peptide, purified from bacteria and immobilized on Protein S Sepharose™ 'pulled down' IGF-IR from 3T3 cell extracts, whereas Protein S Sepharose™ without peptide, or with an irrelevant peptide did not interact with IGF-IR.

Saturation binding of bacterial peptide Int8 to IGF-IR transfected 3T3 cells, and for comparison to parental 3T3 cells, was performed to determine the binding affinity of the Int8

peptide to IGF-1R. Figure 1B shows saturable binding by the RBD Int8 polypeptide that is specific for IGF-IR. The Kd for binding, determined from this and other saturation binding curves was found to be in the nM range (*e.g.*, in the 40 to 150 nM range), which is comparable to the binding affinity of Int8 peptide to HER-2 (Doherty et al., *Supra*) and to EGFR.

The interaction between full-length herstatin and IGF-1R was also investigated. Figure 1C shows that herstatin, purified from transfected S2 insect cells, exhibited dose-dependent binding to IGF-1R at nM concentrations.

Figure 1D shows that full-length herstatin exhibited saturation binding to IGF-IR 3T3 cells, demonstrating nM binding affinity.

These results demonstrate that herstatin and its receptor binding domain bind specifically to IGF-1R with nM binding affinity (*e.g.*, in the 40 to 150 nM range) and that IGF-IR is a target receptor of herstatin.

EXAMPLE 3
(Herstatin was shown to prevent activation of IGF-1R by IGF-1 in MCF7 cells)

According to particular embodiments of the present invention, herstatin blocks activation of IGF-1R by IGF-1 (FIGURES 2A, 2B), and causes IGF-1R down-regulation (FIGURE 2A, lower portion).

Methods. Cell lines, expression vectors, protein purification, pull down assays, antibodies, Western blot analysis and ELISA assays were as described under EXAMPLE I, herein above. IGF-I was added either to MCF-7 breast carcinoma cells, or to an MCF-7/herstatin cell line stably transfected with herstatin, to determine whether herstatin expression affects activation of the IGF-IR by its ligand. MCF7 and MCF7/Hst cells were serum-starved overnight, treated with 5 nM IGF-I over a 60-minute timecourse, and harvested in NP-40 lysis buffer. 1mg of cell lysate was immunoprecipiated with IGF-IRß antibody and protein A agarose beads. Immunoprecipitates were separated on a 10% SDS-PAGE gel and analyzed for IGF-IR expression and tyrosine phosphorylation. Western blots were scanned and quantified by densitometry.

Results. As expected, there is a robust IGF-I-mediated activation of the IGF-IR in MCF7

cells, demonstrated by enhanced tyrosine phosphorylated IGF-IR by 5 min (FIGURE 2A, left panel). In contrast, activation of the IGF-IR by IGF (revealed by receptor tyrosine phosphorylation) was blocked in the herstatin -expressing MCF7 cells (FIGURE 2A, right panel).

These results demonstrate that herstatin modulates IGF-IR-mediated signaling.

Additionally, as shown in FIGURE 2A (lower portion), herstatin not only prevents activation of IGF-1R by IGF-1 in MCF-7 cells (upper panels), but also caused down-regulation of IGF-1R (lower panels). Likewise, herstatin-transfected MCF-7 cells show decreased expression of IRS-2 expression (also important in cell survival) when compared to non-transfected MCF-7 cells (FIGURE 9).

EXAMPLE 4

(The herstatin RBD Int8 polypeptide bound in a specific, dose-dependent manner to EGFR, HER-2, HER-3, HER-4, IGF-1R and ΔEGFR, but did not bind to a mutant form of HER-3, FGFR-3, nor mock-transfected cells)

The binding of the intron 8-encoded RBD, expressed as a bacterial peptide (Int8) was investigated to identify other receptor targets of herstatin. The herstatin RBD Int8 polypeptide bound in a specific, dose-dependent manner to EGFR, HER-2, HER-3, HER-4, IGF-1R and ΔEGFR, but did not bind to a mutant form of HER-3, FGFR-3, or mock-transfected cells (FIGURES 3A and 3B).

Methods. Cell lines, expression vectors, protein purification, pull down assays, antibodies and ELISA assays were as described under EXAMPLE 1, herein above. Briefly, Protein S Sepharose™ with or without immobilized Int 8 peptide, was incubated with extracts from Cos 7 cells transiently transfected with several different receptors (or, in the case of IGF-1 with extracts from hIGFR-1-3T3 cells). Following washing steps, the protein bound to the agarose was analyzed as a Western blot with receptor-specific antibodies.

Results. As previously observed (Doherty et al., *Supra*.; Azios, *Supra*) EGFR and HER-2 from the transfected cell extracts bound specifically to the agarose with Int8 polypeptide (FIGURE 3A). In particular assays, an Int8 peptide with the Arg to Ile mutation at residue 31 was somewhat less efficient in pulling-down the HER-2 receptor from the extracts (on average this herstatin variant appeared to bind about 2-fold less well that the comparable wild type

sequence (SEQ ID NO:24)).

FIGURE 3A also demonstrates that ΔEGFR, a tumor variant of the EGFR missing its N-terminal subdomains I and II (Nishikawa et al., *Proc. Natl. Acad. Sci. USA* 91:7727-31, 1994) specifically associated with Int8 polypeptide.

An additional member of the erbB family, HER-4, was also 'pulled-down' by Int8 agarose.

High-affinity binding by Int8 polypeptide to endogenous HER-3 in MCF7 breast cancer cells was observed, independent of ligand activation (FIGURE 4B). Additionally, binding of the RBD Int8 polypeptide to purified (wild-type) HER-3 ectodomain expressed in stably transfected CHO cells was observed (FIGURE 4C).

However, in the case of one particular form of HER-3 (corresponding to the product of the HER-3 expression vector, a gift from Dr. Tracy Ram, Washington State University in Pullman) there was no detectable association of the expressed HER-3 with Int8 polypeptide agarose, despite abundant expression in the respective transfected cells (FIGURE 3A, third panel from top; and FIGURE 4A). Applicants have determined that this non-Int8 binding form of HER-3 has a single point mutation resulting in substitution of Glu for Gly (relative to accession no.: NM_001982, nucleotide # 1877, and amino acid residue position 560) in the ectodomain of HER-3.

As disclosed in EXAMPLE 2 above with respect to the interaction of the Int8 polypeptide with the IGF-1R, specific 'pull-down' of the β subunit of the IGF-IR from transfected cell extracts was observed (FIGURE 3A, bottom panel). This result may reflect the fact that the IGF-1R contains regions of ectodomain sequence homology with the EGFR (Garrett et al., *Cell* 110:763-73, 2002).

The FGFR-3, a receptor tyrosine kinase with Ig-like motifs and no structural homology with the ErbB family ectodomains, did not bind to the Int8 peptide (FIGURE 3A).

Therefore, according to particular aspects of the present invention, the herstatin RBD Int8 polypeptide binds in a high-affinity, specific manner to EGFR, HER-2, HER-3. HER-4, IGF-1R and ΔEGFR, but does not bind to a mutant form of HER-3 (single point mutation resulting in substitution of Glu for Gly at amino acid position 560), to FGFR-3, or to mock-

transfected cells.

ELISA assay results. ELISA analysis used to quantify bound RBD Int8 polypeptide to further examine interaction of the int8 polypeptide with the extracellular domain of the various receptors at the cell surface. As was shown for the IGF-1R (hIGF-1R-3T3 cells) in EXAMPLE 1 above, FIGURE 3B shows that the Int8 polypeptide bound in a specific and dose-dependent manner to EGFR, HER-2, HER-4, and ΔEGFR, but not to a mutant form of HER-3, FGFR-3, or mock-transfected Cos-7 cells, in agreement with results obtained by the 'pull-down' assays FIGURE 3A).

Binding affinities were further characterized by generating saturation-binding curves (FIGURES 5A and 5B). The RBD Int8 polypeptide bound with high affinity to HER-2-transfected Cos-7 cells (in particular assays, K_D =50 ± 6 nM; FIGURE 5A, open squares; among various assays, in the 40 to 150 nM range) and to EGFR-transfected Cos-7 cells (in particular K_D=78±10 nM; FIGURE 5A, filled squares; among various assays in the 40 to 150 nM range) with binding affinities, assessed by comparative nonlinear regression analysis, that were not significantly different (*P*=0.40) (FIGURE 5A). Furthermore, similar to the determination of EXAMPLE 2 above (K_D = 40nM in particular assays; among various assays in the 40 to 150 nM range), the RBD Int8 polypeptide bound to the IGF-IR/3T3 cells with an affinity (K_D = 70±21 in particular assays; among various assays in the 40 to 150 nM range) that was not significantly different (*P*=0.96) from the affinity for HER-2/3T3 cells (K_D=66± 16) (FIGURE 5B) (among various assays in the 40 to 150 nM range).

In particular assays, the mutant Int8 polypeptide with Arg31Ile bound somewhat less well (perhaps 2-fold) to the HER-2 receptor overexpressing cells, even though the herstatin ELISA detected the wildtype and mutant peptide equally.

These results show, therefore, that the RBD Int8 polypeptide bound to EGFR, HER-2, and IGF-1R with similar (overlapping) binding affinities.

EXAMPLE 5

(Relative binding of herstatin between 3T3/HER-2 and 3T3/IGF-IR cells, and between 3T3/HER-2 and Cos-7/EGFcells was directly compared, and the relative affinities of herstatin and RGB Int8 polypeptide were determined on 3T3/HER-2 cells)

ELISA analysis was performed to compare relative binding of herstatin between 3T3/HER-2 and 3T3/IGF-IR cells, and between 3T3/HER-2 and Cos-7/EGFcells. Additionally, the relative affinities of herstatin and RGB Int8 polypeptide were determined on 3T3/HER-2 cells.

Methods. Cell lines, expression vectors, protein purification, antibodies and ELISA assays were as described under EXAMPLE 1, herein above.

Results. A direct comparison of the binding of herstatin to 3T3/HER-2 and 3T3/IGF-IR cells revealed that the affinity for the IGF-1R (K_D ~151 nM) was lower ($P<.0001$) by about 10-fold (FIGURE 6A). The full-length herstatin bound to 3T3/HER-2 cells with a K_D = 14.7 ±1.8 nM, which is greater than the binding affinity of RBD Int8 polypeptide ($P<.0001$) by 3-4 fold (FIGURE 6A).

The dissociation constant of FIGURE 6A for EGFR was similar to that of HER-2, and was unaffected by ligand occupation indicated by a K_D = 16.4 ± 3.6 nM versus 16.3 ±3.6 nM (respectively) for Cos-7/EGFR treated or not with 10 nM EGF (FIGURE 6B).

EXAMPLE 6

(Herstatin exhibited saturation binding to endogenous receptors in A431 epidermoid carcinoma cells)

Herstatin binding to endogenous receptors in A431 epidermoid carcinoma cells was investigated to determine if a one-affinity site binding model was the best fit for EGFR-specific binding of herstatin, in the presence and absence of EGF.

Methods. A431 cells were from ATCC.

Results. Herstatin exhibited saturation binding to endogenous receptors in A431 epidermoid carcinoma cells, which express very high levels of EGFR and low levels of other ErbB receptors (FIGURE 6C). At saturation, 6.9 ±0.4 pmol of herstatin were bound indicating about 2 x 10^6 binding sites/cell, which matches the number of EGFR per A431 cell at 2 x 10^6 (Filmus et al., *Biochem. Biophys. Res. Commun.*, 131:207-15, 1985; Filmus et al., *Biochem. Biophys. Res. Commun.* 128:898-905, 1985). Comparison of nonlinear models indicated that a hyperbolic one-affinity site binding model was the best fit for EGFR-specific binding of herstatin, in the presence and absence of EGF.

EXAMPLE 7

(Herstatin effects were shown to be receptor specific)

Because herstatin binds to multiple receptors, binding studies were performed to demonstrate that the effects of herstatin are receptor-specific.

Methods. Cells and western blot analysis were as described under EXAMPLE 1 above.

Results. As demonstrated herein above, herstatin does not bind to the FGFR. FIGURE 7A (upper panel) and FIGURE 7D show that herstatin blocks intracellular signaling (MAPK phosphorylation) by Heregulin (the ligand for HER-3 and HER-4) and EGF (the ligand for the EGFR), respectively, in MCF-7 cells, whereas herstatin does not affect FGF signaling (MAPK phosphorylation) in MCF-7 cells (FIGURE 7A, lower panel), and does not inhibit IGF-1-mediated ERK phosphorylation in MCF-7 cells (FIGURE 7B).

Additionally, FIGURE 7C shows that herstatin down-regulates HER-1, HER-3 and HER-4 receptors in MCF-7 cells.

EXAMPLE 8

(Herstatin inhibited Heregulin/HER-4-mediated activation of, and IGF-1/IGF1R-mediated activation of the PI3/Akt pathway that is important in cell survival)

The physiological effects of herstatin on HER-4-mediated signaling were investigated. The protein kinase called Akt is a key regulator of cellular survival. Activation of Akt is both necessary and sufficient for survival of cells. Stimulation of activated Akt causes inappropriate cell survival, or prevents normal cell death, which has been found to occur in several human cancers. HER-2 and the EGF receptor, for example, both cause activation of the Akt survival signal whereby, according to current theory and belief, they cause oncogenic growth (Blume-Jensen & Hunter, *Nature* 411:355-365, 2001; Datta et al., *Genes and Development* 13:2905-2907, 2000; and Yarden & Slikowski, Nature Reviews, *Molecular Cell Biology*, 2:127-137).

Methods. Measurement of activated phospho-akt (activated AKT) in EGFR3T3 cells. Measurement of activated AKT (phospho-akt) was accomplished using standard Western blotting techniques, employing a commercially available anti-phospho-akt antibody (Santa Cruz). Briefly, CHO cells were transfected with HER-4 alone, or cotransfected with HER-4 and and herstatin. Twenty-four (24) hours after transfection, serum-starved cells were treated with

heregulin or vehicle for 15 and 30 min. The cells were extracted and analyzed as a Western blot with antibodies specific for activated Akt (anti-phospho-Akt), or for total Akt.

Results. Heregulin caused a robust increase in phospho-Akt in the absence of herstatin, whereas heregulin induction of phosphoAkt was reduced in herstatin expressing cells.

Additionally, as shown in FIGURE 8, herstatin inhibited IGF-1/IGF-1R-mediated activation of the PI3/Akt pathway.

Furthermore, FIGURE 9 shows the effect of herstatin -expression on the expression levels of various signaling proteins. Herstatin expression in MCF7 breast carcinoma cells down-regulated IGF-1R, IRS-1, IRS-2 (also important in cell survival), and pKB/Akt expression, but MAPK expression was unaffected. Herstatin expression also induced expression of the p66 isoform of Shc, which is not detectable by Western Blot in parental MCF7 cells.

Therefore, according to particular aspects of the present invention, herstatin inhibits activation of the PI3/Akt and IRS-2 pathways that are important in cell survival.

EXAMPLE 9

(Herstatin inhibited IGF-1-mediated survival of MCF7 cells)

Previous studies have shown that stable expression of herstatin in MCF7 breast carcinoma cells resulted in diminished heregulin-stimulated proliferation (Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003). To further investigate the effect of herstatin on IGF-I action, the IGF-I-induced growth of parental MCF7 cells and two clones stably transfected with herstatin (MCF7/Hst#1 and MCF7/Hst#2) was investigted.

Methods. MCF7 parental and MCF7/Hst breast cancer cells, stably transfected with herstatin (either MCF7/Hst#1, a low-level herstatin -expressing clone, or MCF7/Hst#2, a relatively high-level herstatin -expressing clone), were plated into 24-well plates at 40,000 cells per well overnight and the MTS assay was conducted in triplicate wells to quantify viable cells at time zero. The cells were then treated in serum-free media with vehicle or with 10 nM IGF-I and triplicate wells were quantified by the MTS assay on day 1, 2 and 3. The results are plotted as mean percent of the start at zero time. The error bars represent the standard error of the mean.

Results. FIGURE 10A and 10B show that herstatin expression blocks IGF-1-mediated survival of MCF7 cells. Parental MCF7 cells grew in response to IGF-I, whereas cell viability

decreased in the absence of growth factor. Both of the MCF7/Hst clones, however, failed to exhibit IGF-I-stimulated growth. Furthermore, the growth reduction occurred faster in clone #1, which expresses relatively more herstatin, indicating that herstatin affects IGF-I-mediated growth in a concentration-dependent manner.

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CLAIMS

1. A method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of a herstatin, or of a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

2. The method of claim 1, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2.

3. The method of claims 1 or 2, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

4. The method of claims 1 or 2, wherein the herstatin, or variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

5. A method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of an Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of: □EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

6. The method of claim 5, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

7. The method of claim 5 or 6, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

8. The method of claims 5 or 6, wherein the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity

binding constant of at least 10^7 M^{-1}.

9. The method of any of claims 1-8, wherein the condition is a cellular proliferative condition or disorder.

10. The method of any of claims 1-9, wherein the condition is cancer.

11. The method of claim 10, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colon, lung cancer, glioblastoma ovarian cancer, pancreatic cancer and prostate cancer.

12. The method of any of claims 1-11, wherein the target cell does not express EGFR (HER-1, erbB-1) or HER-2 (erbB-2), or does not express either.

13. The method of claims 10 or 11, wherein the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different from herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants.

14. The method of claim 13, wherein the cancer is breast cancer, or prostate cancer.

15. The method of claim 13, wherein the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

16. The method of any of claims 1-15, further comprising administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell.

17. The method of claim 16, wherein the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

18. The method of claim 17, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

19. The method of claim 16, wherein the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the Herstatin, or the variant thereof.

20. The method of any of claims 1-19, further comprising administration of a

therapeutically effective amount of a chemotherapeutic agent.

21. The method of claim 20, wherein the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramide, triethylenethiophosphoramide, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedepa, uredepa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

22. A method for conferring to a therapeutic agent the capacity to be targeted to a target cell, wherein the target cell is characterized by expression of at least one target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, comprising attaching the therapeutic agent to herstatin, or to a variant thereof, that binds to the extracellular domain of the at least one target receptor.

23. The method of claim 22, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2

24. The method of claims 22 or 23, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

25. The method of claims 22 or 22, wherein the herstatin, or variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

26. A method for targeting a therapeutic agent to target cells, comprising attaching the therapeutic agent to an Int8 RBD polypeptide, or to a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell being targeted, wherein the at

least one target receptor is selected from the group consisting of: □EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

27. The method of claim 26, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

28. The method of claim 26 or 27, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

29. The method of claims 26 or 27, wherein the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

30. The method of any of claims 22-29, wherein the target cell is a cancer cell.

31. The method of claim 30, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colon, lung cancer, glioblastoma ovarian cancer, pancreatic cancer and prostate cancer.

32. The method of any of claims 22-31, wherein the target cell does not express EGFR (HER-1, erbB-1) or HER-2 (erbB-2), or does not express either.

33. A pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a first agent selected from the group consisting of: herstatin, or a variant thereof; a Int8 RBD polypeptide, or a variant thereof; and combinations thereof, the composition further comprising a second agent selected from the group consisting of: a receptor-specific antibody that binds to the extracellular domain (ECD) of a cellular receptor of the target cell; a small molecule receptor tyrosine kinase inhibitor; and combinations thereof, with the proviso that the receptor-specific antibody is not a HER-1 (EGFR) or HER-2-specific antibody.

34. The composition of claim 33, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2.

35. The composition of claims 33 or 34, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

36. The composition of claims 33, wherein the Int8 RBD polypeptide, or a variant thereof comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

37. The composition of claim 33 or 36, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

38. The composition of any of claims 33-37, wherein the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

39. The composition of claim 38, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

40. Use of a herstatin, or of a variant thereof, that binds to the extracellular domain of at least one target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, for the manufacture of a medicament for treating a condition characterized by altered expression of, or altered intracellular signaling mediated by the at least one target receptor.

41. The use of claim 40, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2

42. The use of claims 40 or 41, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

43. The use of claims 40 or 41, wherein the herstatin, or variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

44. Use of a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, for the manufacture of a medicament for treating a

condition characterized by altered expression of, or altered intracellular signaling mediated by the at least one target receptor.

45. The use of claim 44, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

46. The use of claim 44 or 45, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

47. The use of claims 44 or 45, wherein the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least 10^7 M^{-1}.

48. The use of any of claims 40-47, wherein the condition is a cellular proliferative condition or disorder.

49. The use of any of claims 40-48, wherein the condition is cancer.

50. The use of any of claims 40-49, wherein the target cell does not express EGFR (HER-1, erbB-1) or HER-2 (erbB-2), or does not express either.

51. The method of claim 50, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colon, lung cancer, glioblastoma ovarian cancer, pancreatic cancer and prostate cancer.

52. The use of any one of claims 49-51, wherein the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different from herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants.

53. The use of claim 52, wherein the cancer is breast cancer or prostate cancer.

54. The use of claim 52, wherein the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

55. The use of claim 54, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

56. The use of any of claims 40-53, further comprising administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell.

57. The use of claim 56, wherein the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1); ΔEGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

58. The use of claim 57, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

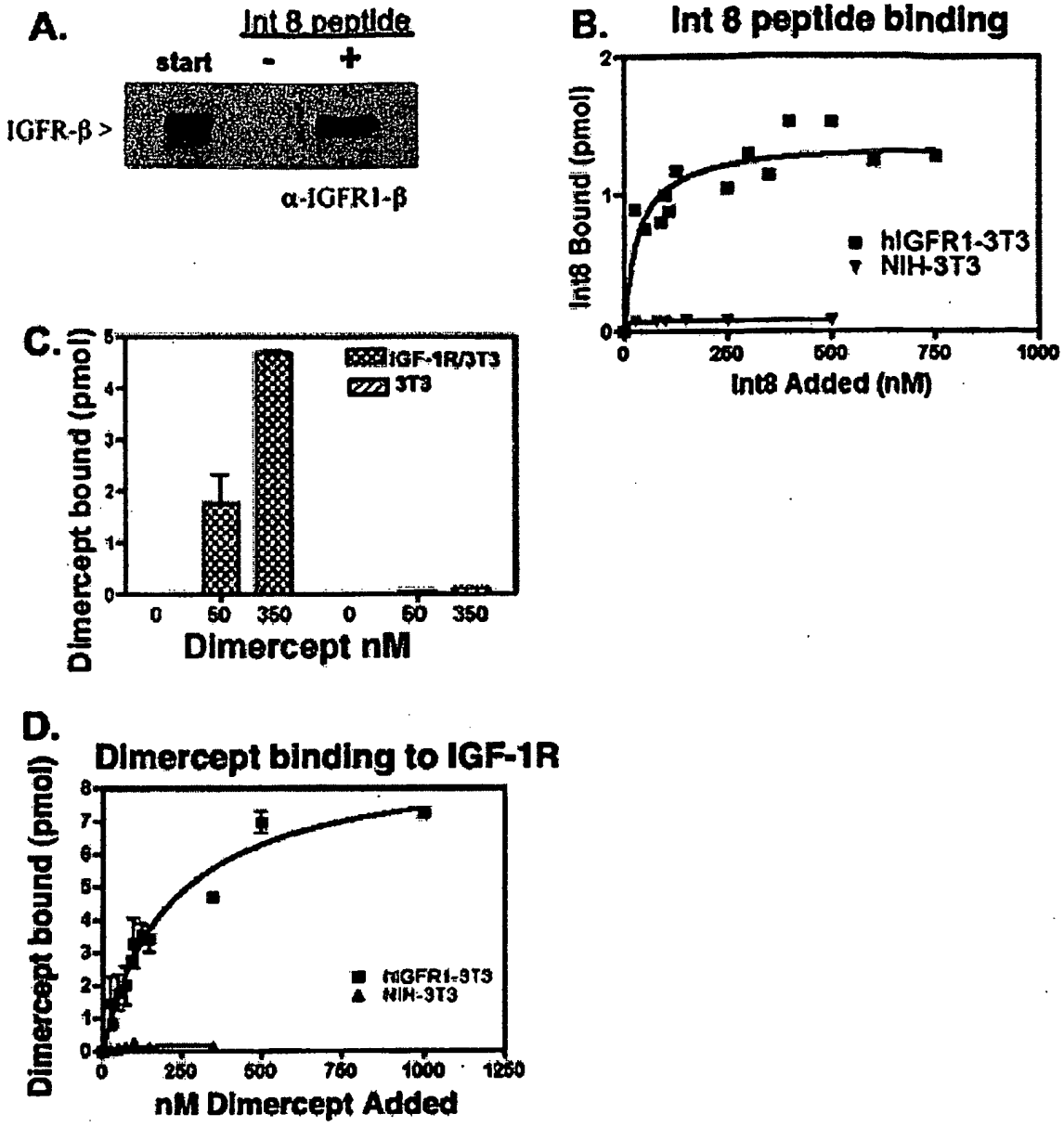
59. The use of claim 56, wherein the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the Herstatin, or the variant thereof.

60. The use of any of claims 40-59, further comprising administration of a therapeutically effective amount of a chemotherapeutic agent.

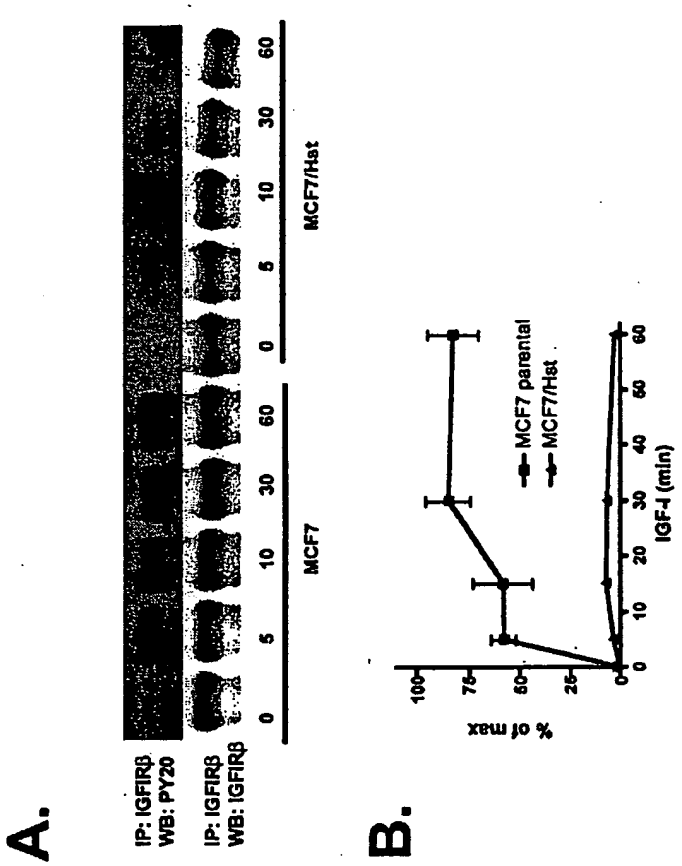
61. The use of claim 60, wherein the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramide, triethylenethiophosphoramide, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedepa, uredepa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

62. A method for identification of cells having HER-3 receptors that do not bind herstatin, int 8 RDB polypeptides, or variants thereof, comprising: obtaining a cellular sample; and determining, using one or more suitable assays, whether the cells express SEQ ID NO:14, wherein cells having HER-3 receptors that do not bind herstatin are identified if SEQ ID NO:14 is expressed.

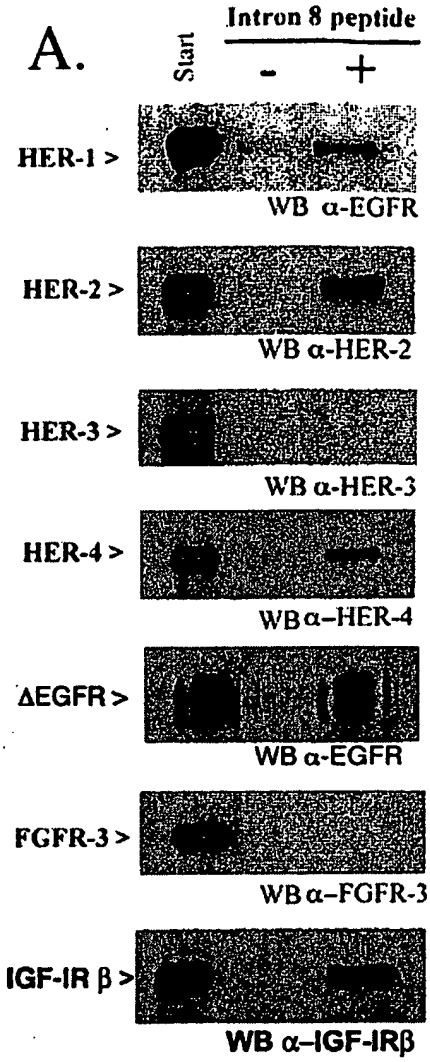
63. A method for screening for cells that are, at least to some extent, non-responsive to herstatin, int 8 RDB polypeptides, or variants thereof, comprising obtaining a cellular sample; and determining, using one or more suitable assays, whether the cells express SEQ ID NO:14, wherein the cells are determined to be, at least to some extent, non-responsive to herstatin, int 8 RDB polypeptes, or variants thereof, if the cells express SEQ ID NO:14.

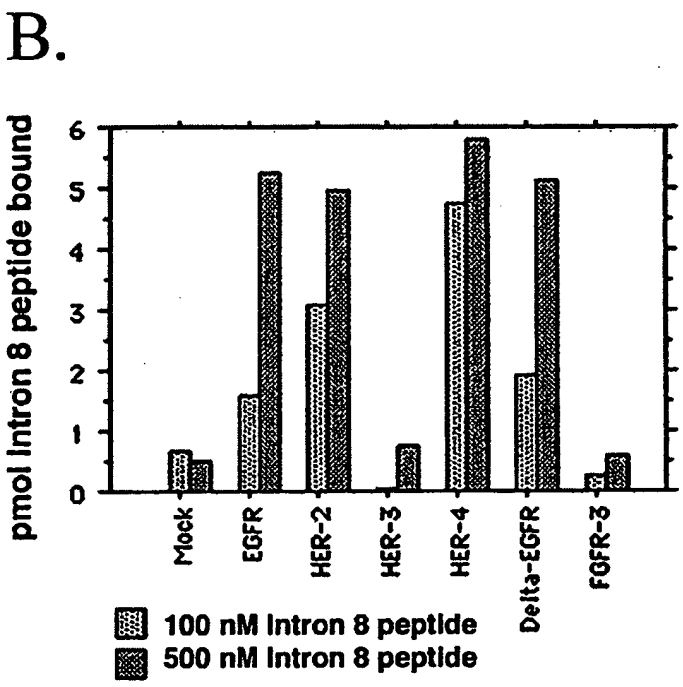


FIGURES 1A, 1B, 1C and 1D

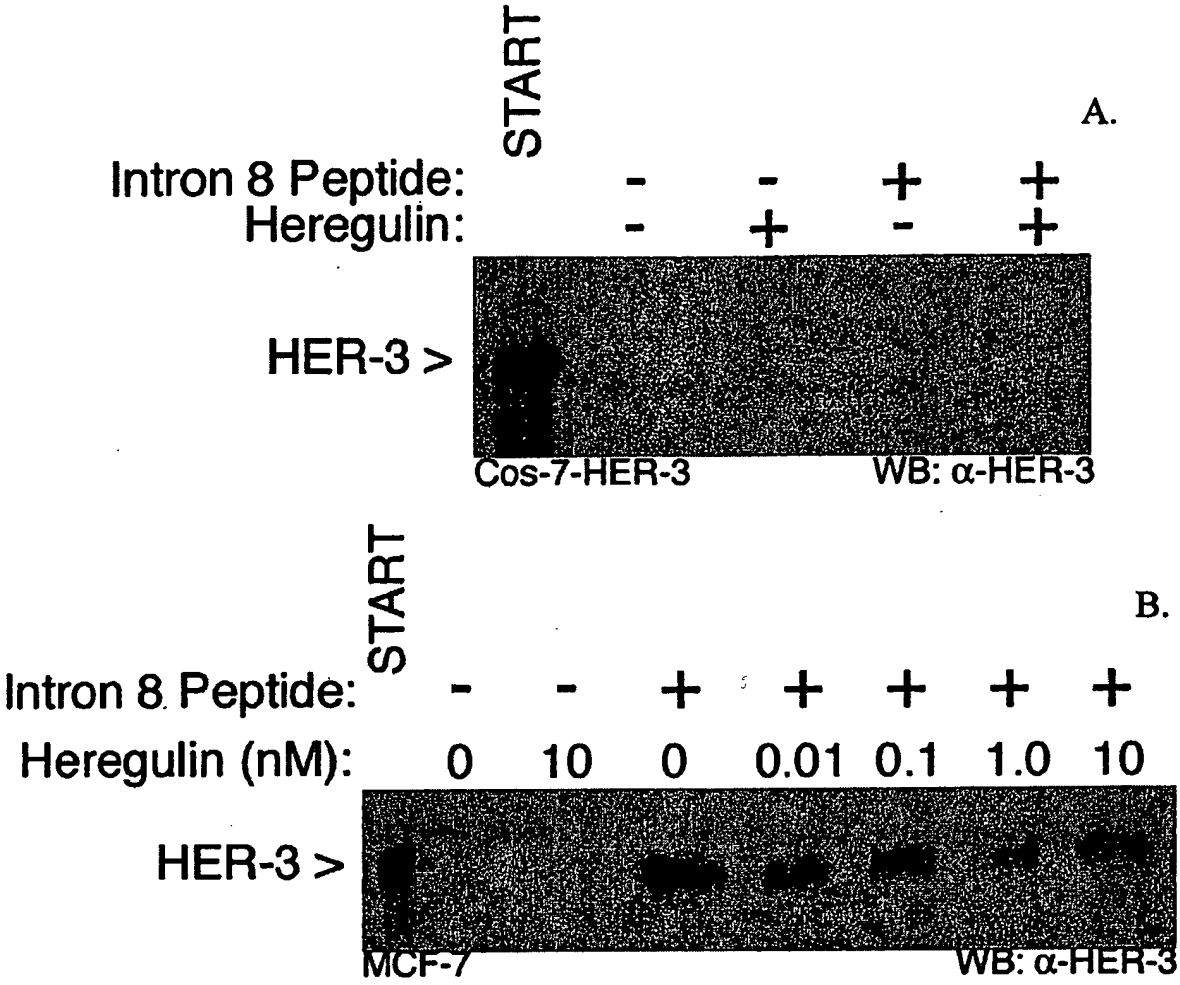


Figures 2A and 2B





FIGURES 3A, and 3B



FIGURES 4A and 4B

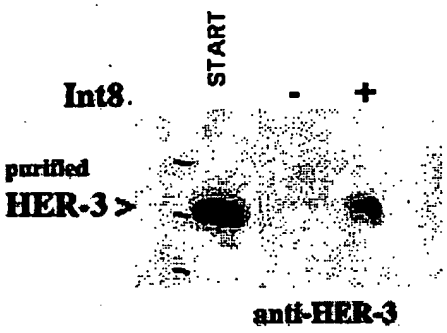
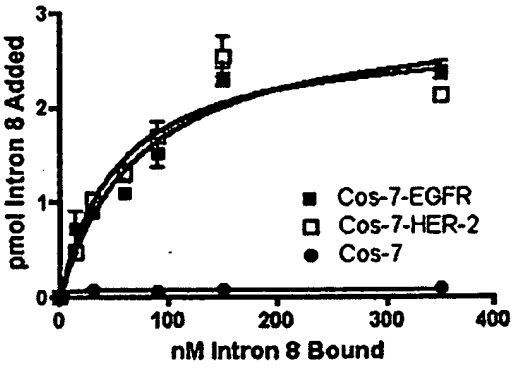
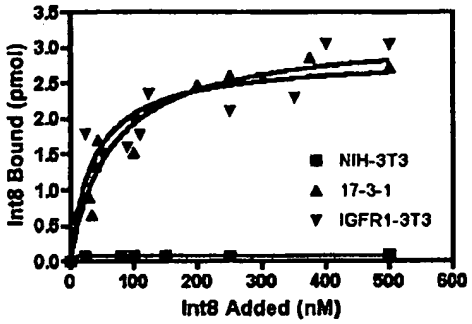


FIGURE 4C

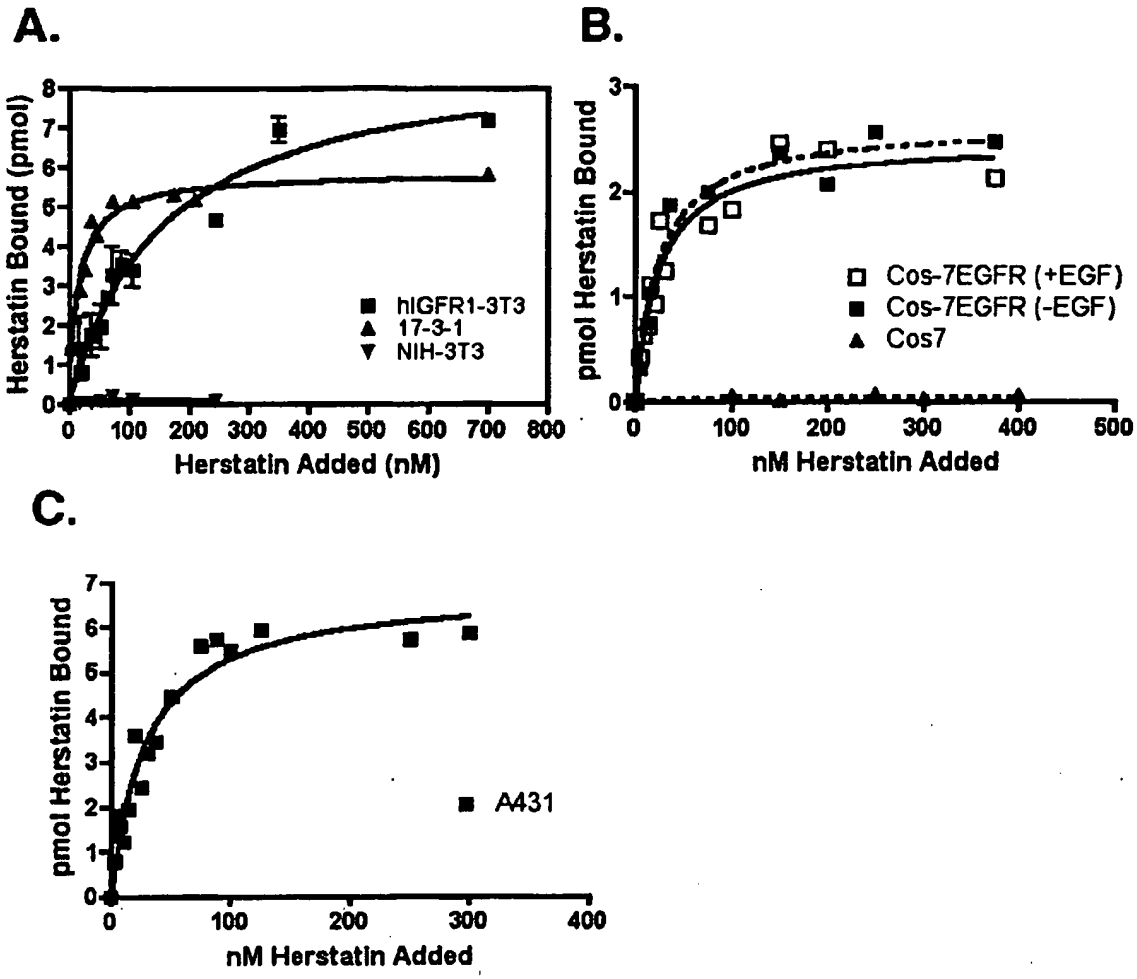
A



B.



FIGURES 5A and 5B



FIGURES 6A, 6B and 6C

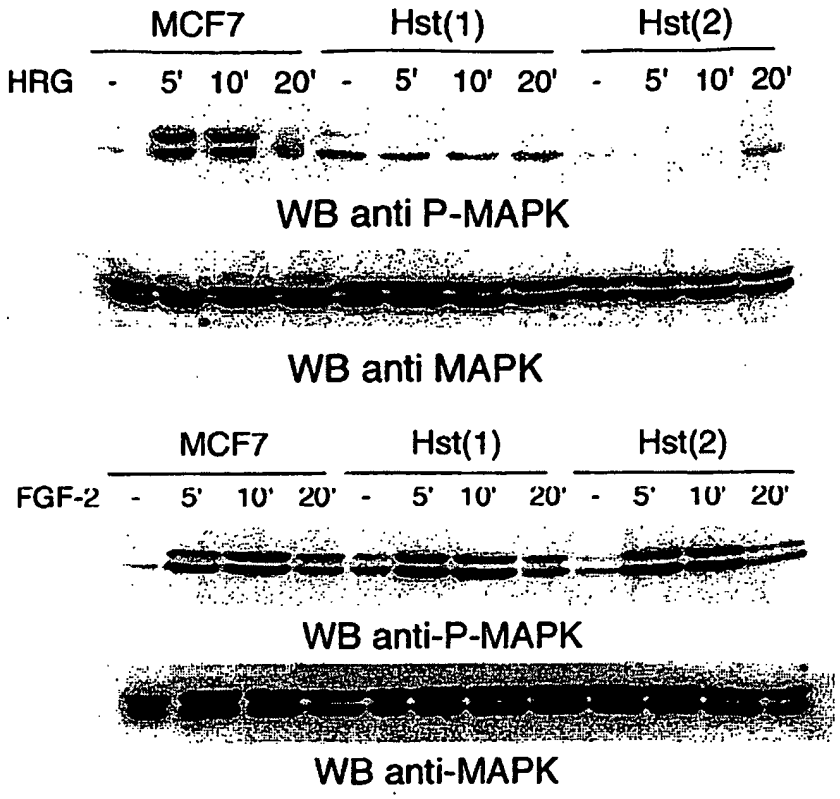

MCF7
Hst(1)
Hst(2)
HRG - 5' 10' 20' - 5' 10' 20' - 5' 10' 20'
WB anti P-MAPK
WB anti MAPK
MCF7
Hst(1)
Hst(2)
FGF-2 - 5' 10' 20' - 5' 10' 20' - 5' 10' 20'
WB anti-P-MAPK
WB anti-MAPK

FIGURE 7A

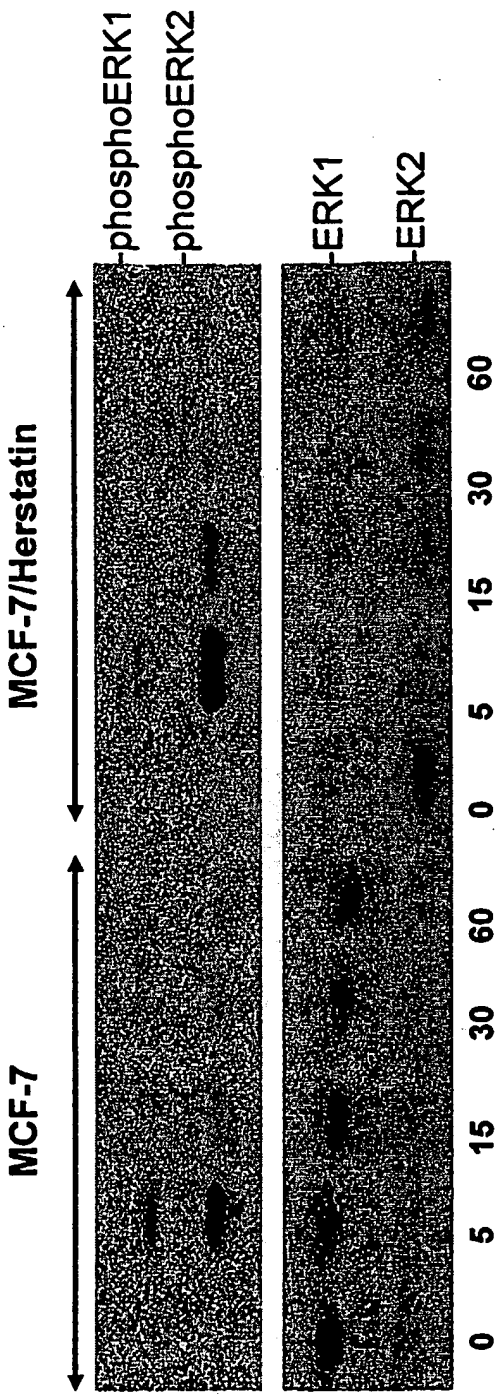
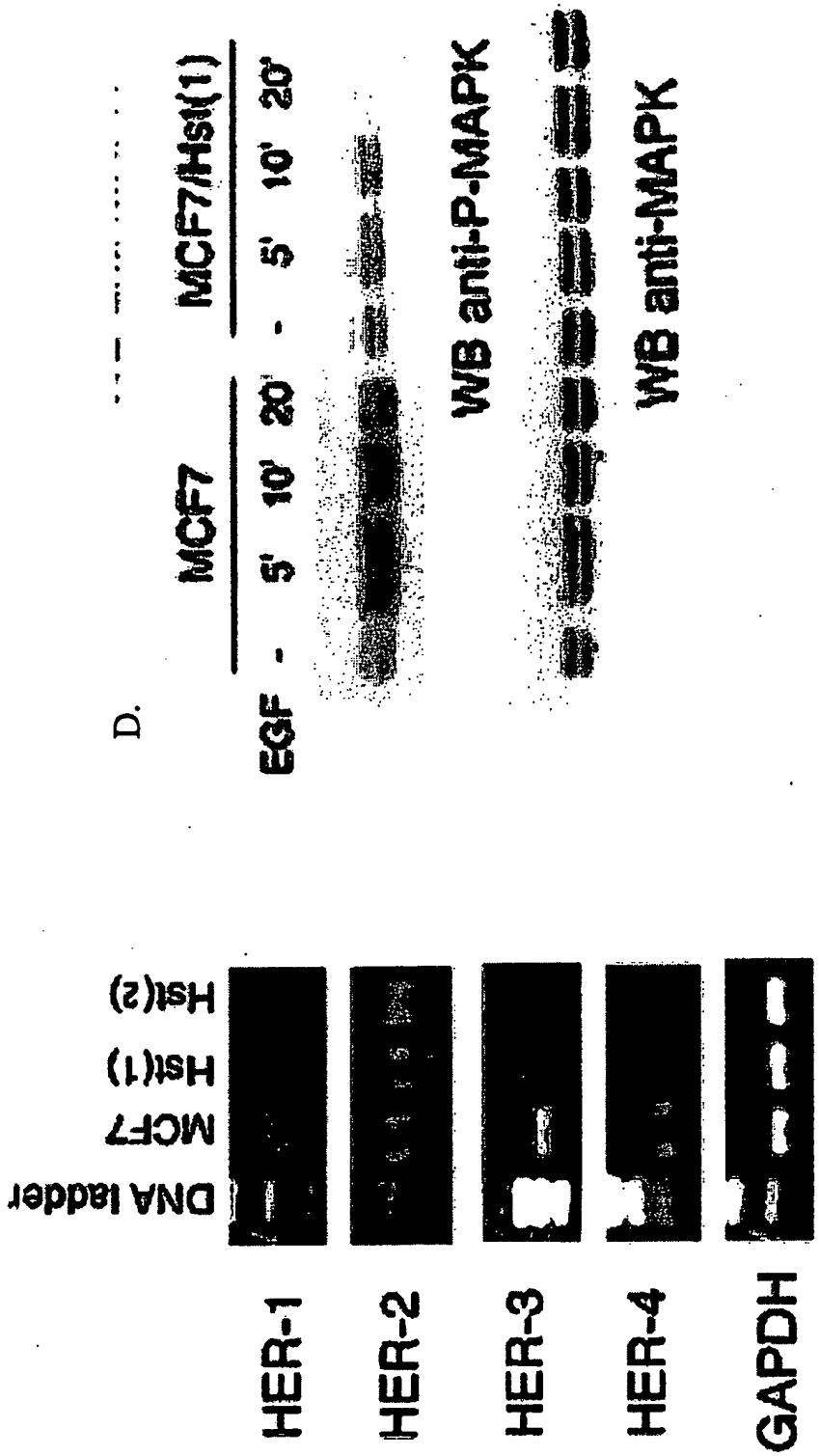
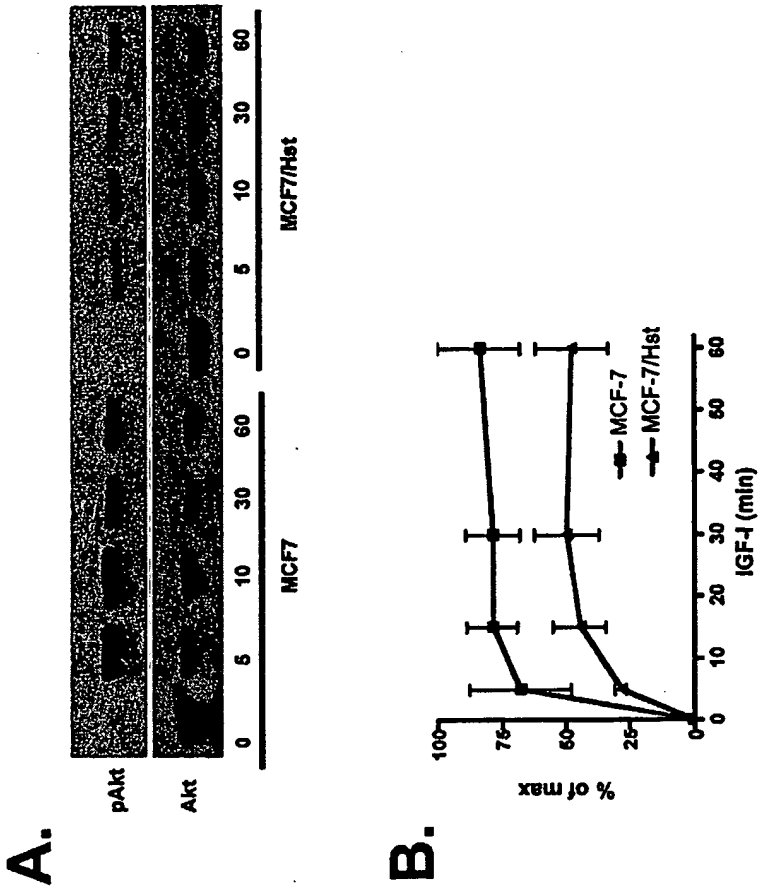

phosphoERK1
phosphoERK2
ERK1
ERK2
MCF-7/Herstatin
MCF-7
0
5
15
30
60
0
5
15
30
60

FIGURE 7B



FIGURES 7C and 7D



Figures 8A and 8B

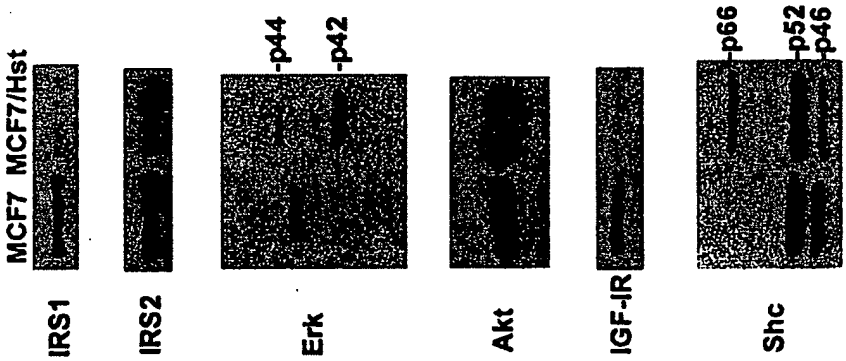
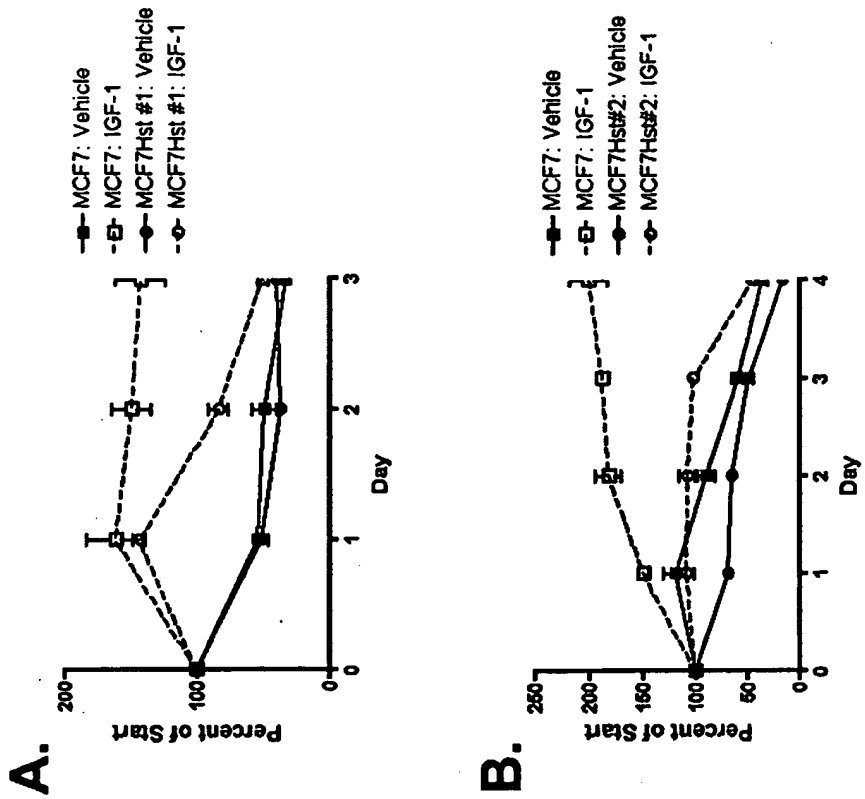


Figure 9



Figures 10A and 10B

SEQUENCE LISTING

<110> OREGON HEALTH & SCIENCE UNIVERSITY
Clinton, Gail M.
Shamieh, Lara

<120> COMPOSITIONS AND METHODS FOR MODULATING SIGNALING BY IGF-1 RECEPTOR AND ERBB RECEPTORS

<130> 49321-137

<150> US 60/590,473
<151> 2004-07-23

<150> US 60/564,893
<151> 2004-04-22

<160> 24

<170> PatentIn version 3.3

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Xaa Xaa Gln Pro Xaa Pro Ala His Pro Val Leu Ser Phe Leu Xaa Pro
20 25 30

Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Xaa Ile Ser Pro Val Ser Val Gly Arg Gly Xaa
50 55 60

Asp Pro Asp Ala His Val Ala Val Xaa Leu Ser Arg Tyr Glu Gly

65 70 75

<210> 2
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<220>
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20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Arg Arg Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

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Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145                 150                 155                 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
                165                 170                 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
            180                 185                 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
        195                 200                 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
    210                 215                 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225                 230                 235                 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
                245                 250                 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
            260                 265                 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
        275                 280                 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
    290                 295                 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305                 310                 315                 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
                325                 330                 335

Pro Cys Ala Arg Gly Xaa His Ser Xaa Xaa Pro Arg Pro Ala Ala Val
            340                 345                 350

Pro Val Pro Xaa Xaa Xaa Gln Pro Xaa Pro Ala His Pro Val Leu Ser
        355                 360                 365

Phe Leu Xaa Pro Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro
    370                 375                 380
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Gly Arg Gly Xaa Asp Pro Asp Ala His Val Ala Val Xaa Leu Ser Arg
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Tyr Glu Gly

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Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
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Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Ile Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75

<210> 4
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Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
355 360 365

Phe Leu Ile Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
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Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
405 410 415

Tyr Glu Gly

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<213> Homo sapiens

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aggccacctc gtcggcgtcc gcccgagtcc ccgcctcgcc gccaacgcca caaccaccgc 180

gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgagc tcttcgggga 240

gcagcg atg cga ccc tcc ggg acg gcc ggg gca gcg ctc ctg gcg ctg 288
Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu
1 5 10

ctg gct gcg ctc tgc ccg gcg agt cgg gct ctg gag gaa aag aaa gtt 336
Leu Ala Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val
15 20 25 30

tgc caa ggc acg agt aac aag ctc acg cag ttg ggc act ttt gaa gat 384
Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp
35 40 45

cat ttt ctc agc ctc cag agg atg ttc aat aac tgt gag gtg gtc ctt 432
His Phe Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu
50 55 60

ggg aat ttg gaa att acc tat gtg cag agg aat tat gat ctt tcc ttc 480
Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe
65 70 75

tta aag acc atc cag gag gtg gct ggt tat gtc ctc att gcc ctc aac 528
Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn
80 85 90

aca gtg gag cga att cct ttg gaa aac ctg cag atc atc aga gga aat 576
Thr Val Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn
95 100 105 110

atg tac tac gaa aat tcc tat gcc tta gca gtc tta tct aac tat gat 624
Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp
115 120 125

gca aat aaa acc gga ctg aag gag ctg ccc atg aga aat tta cag gaa 672
Ala Asn Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu
130 135 140

atc ctg cat ggc gcc gtg cgg ttc agc aac aac cct gcc ctg tgc aac 720
Ile Leu His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn
145 150 155

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gtg gag agc atc cag tgg cgg gac ata gtc agc agt gac ttt ctc agc      768
Val Glu Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser
    160                 165                 170

aac atg tcg atg gac ttc cag aac cac ctg ggc agc tgc caa aag tgt      816
Asn Met Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys
175                 180                 185                 190

gat cca agc tgt ccc aat ggg agc tgc tgg ggt gca gga gag gag aac      864
Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn
                195                 200                 205

tgc cag aaa ctg acc aaa atc atc tgt gcc cag cag tgc tcc ggg cgc      912
Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg
            210                 215                 220

tgc cgt ggc aag tcc ccc agt gac tgc tgc cac aac cag tgt gct gca      960
Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala
        225                 230                 235

ggc tgc aca ggc ccc cgg gag agc gac tgc ctg gtc tgc cgc aaa ttc     1008
Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe
    240                 245                 250

cga gac gaa gcc acg tgc aag gac acc tgc ccc cca ctc atg ctc tac     1056
Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr
255                 260                 265                 270

aac ccc acc acg tac cag atg gat gtg aac ccc gag ggc aaa tac agc     1104
Asn Pro Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser
                275                 280                 285

ttt ggt gcc acc tgc gtg aag aag tgt ccc cgt aat tat gtg gtg aca     1152
Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr
            290                 295                 300

gat cac ggc tcg tgc gtc cga gcc tgt ggg gcc gac agc tat gag atg     1200
Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met
        305                 310                 315

gag gaa gac ggc gtc cgc aag tgt aag aag tgc gaa ggg cct tgc cgc     1248
Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg
    320                 325                 330

aaa gtg tgt aac gga ata ggt att ggt gaa ttt aaa gac tca ctc tcc     1296
Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser
335                 340                 345                 350

ata aat gct acg aat att aaa cac ttc aaa aac tgc acc tcc atc agt     1344
Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser
                355                 360                 365

ggc gat ctc cac atc ctg ccg gtg gca ttt agg ggt gac tcc ttc aca     1392
Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr
            370                 375                 380

cat act cct cct ctg gat cca cag gaa ctg gat att ctg aaa acc gta     1440
His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val
        385                 390                 395
```

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aag gaa atc aca ggg ttt ttg ctg att cag gct tgg cct gaa aac agg      1488
Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg
    400                 405                 410

acg gac ctc cat gcc ttt gag aac cta gaa atc ata cgc ggc agg acc      1536
Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr
415                 420                 425                 430

aag caa cat ggt cag ttt tct ctt gca gtc gtc agc ctg aac ata aca      1584
Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr
                435                 440                 445

tcc ttg gga tta cgc tcc ctc aag gag ata agt gat gga gat gtg ata      1632
Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile
            450                 455                 460

att tca gga aac aaa aat ttg tgc tat gca aat aca ata aac tgg aaa      1680
Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys
        465                 470                 475

aaa ctg ttt ggg acc tcc ggt cag aaa acc aaa att ata agc aac aga      1728
Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg
    480                 485                 490

ggt gaa aac agc tgc aag gcc aca ggc cag gtc tgc cat gcc ttg tgc      1776
Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys
495                 500                 505                 510

tcc ccc gag ggc tgc tgg ggc ccg gag ccc agg gac tgc gtc tct tgc      1824
Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys
                515                 520                 525

cgg aat gtc agc cga ggc agg gaa tgc gtg gac aag tgc aac ctt ctg      1872
Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu
            530                 535                 540

gag ggt gag cca agg gag ttt gtg gag aac tct gag tgc ata cag tgc      1920
Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys
        545                 550                 555

cac cca gag tgc ctg cct cag gcc atg aac atc acc tgc aca gga cgg      1968
His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg
    560                 565                 570

gga cca gac aac tgt atc cag tgt gcc cac tac att gac ggc ccc cac      2016
Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His
575                 580                 585                 590

tgc gtc aag acc tgc ccg gca gga gtc atg gga gaa aac aac acc ctg      2064
Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu
                595                 600                 605

gtc tgg aag tac gca gac gcc ggc cat gtg tgc cac ctg tgc cat cca      2112
Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro
            610                 615                 620

aac tgc acc tac gga tgc act ggg cca ggt ctt gaa ggc tgt cca acg      2160
Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr
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        625                 630                 635

aat ggg cct aag atc ccg tcc atc gcc act ggg atg gtg ggg gcc ctc     2208
Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu
    640                 645                 650

ctc ttg ctg ctg gtg gtg gcc ctg ggg atc ggc ctc ttc atg cga agg     2256
Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg
655                 660                 665                 670

cgc cac atc gtt cgg aag cgc acg ctg cgg agg ctg ctg cag gag agg     2304
Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg
                675                 680                 685

gag ctt gtg gag cct ctt aca ccc agt gga gaa gct ccc aac caa gct     2352
Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala
            690                 695                 700

ctc ttg agg atc ttg aag gaa act gaa ttc aaa aag atc aaa gtg ctg     2400
Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu
        705                 710                 715

ggc tcc ggt gcg ttc ggc acg gtg tat aag gga ctc tgg atc cca gaa     2448
Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu
    720                 725                 730

ggt gag aaa gtt aaa att ccc gtc gct atc aag gaa tta aga gaa gca     2496
Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala
735                 740                 745                 750

aca tct ccg aaa gcc aac aag gaa atc ctc gat gaa gcc tac gtg atg     2544
Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met
                755                 760                 765

gcc agc gtg gac aac ccc cac gtg tgc cgc ctg ctg ggc atc tgc ctc     2592
Ala Ser Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu
            770                 775                 780

acc tcc acc gtg cag ctc atc acg cag ctc atg ccc ttc ggc tgc ctc     2640
Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu
        785                 790                 795

ctg gac tat gtc cgg gaa cac aaa gac aat att ggc tcc cag tac ctg     2688
Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu
    800                 805                 810

ctc aac tgg tgt gtg cag atc gca aag ggc atg aac tac ttg gag gac     2736
Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp
815                 820                 825                 830

cgt cgc ttg gtg cac cgc gac ctg gca gcc agg aac gta ctg gtg aaa     2784
Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys
                835                 840                 845

aca ccg cag cat gtc aag atc aca gat ttt ggg ctg gcc aaa ctg ctg     2832
Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu
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ggt gcg gaa gag aaa gaa tac cat gca gaa gga ggc aaa gtg cct atc     2880
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Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile
        865                 870                 875

aag tgg atg gca ttg gaa tca att tta cac aga atc tat acc cac cag     2928
Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln
    880                 885                 890

agt gat gtc tgg agc tac ggg gtg acc gtt tgg gag ttg atg acc ttt     2976
Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe
895                 900                 905                 910

gga tcc aag cca tat gac gga atc cct gcc agc gag atc tcc tcc atc     3024
Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile
                915                 920                 925

ctg gag aaa gga gaa cgc ctc cct cag cca ccc ata tgt acc atc gat     3072
Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp
            930                 935                 940

gtc tac atg atc atg gtc aag tgc tgg atg ata gac gca gat agt cgc     3120
Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg
        945                 950                 955

cca aag ttc cgt gag ttg atc atc gaa ttc tcc aaa atg gcc cga gac     3168
Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp
    960                 965                 970

ccc cag cgc tac ctt gtc att cag ggg gat gaa aga atg cat ttg cca     3216
Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro
975                 980                 985                 990

agt cct aca gac tcc aac ttc tac cgt gcc  ctg atg gat gaa gaa  gac   3264
Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala  Leu Met Asp Glu Glu  Asp
                995                 1000                1005

atg gac gac gtg  gtg gat gcc gac gag  tac ctc atc cca cag  cag      3309
Met Asp Asp Val  Val Asp Ala Asp Glu  Tyr Leu Ile Pro Gln  Gln
            1010                1015                1020

ggc ttc ttc agc  agc ccc tcc acg tca  cgg act ccc ctc ctg  agc      3354
Gly Phe Phe Ser  Ser Pro Ser Thr Ser  Arg Thr Pro Leu Leu  Ser
            1025                1030                1035

tct ctg agt gca  acc agc aac aat tcc  acc gtg gct tgc att  gat      3399
Ser Leu Ser Ala  Thr Ser Asn Asn Ser  Thr Val Ala Cys Ile  Asp
            1040                1045                1050

aga aat ggg ctg  caa agc tgt ccc atc  aag gaa gac agc ttc  ttg      3444
Arg Asn Gly Leu  Gln Ser Cys Pro Ile  Lys Glu Asp Ser Phe  Leu
            1055                1060                1065

cag cga tac agc  tca gac ccc aca ggc  gcc ttg act gag gac  agc      3489
Gln Arg Tyr Ser  Ser Asp Pro Thr Gly  Ala Leu Thr Glu Asp  Ser
            1070                1075                1080

ata gac gac acc  ttc ctc cca gtg cct  gaa tac ata aac cag  tcc      3534
Ile Asp Asp Thr  Phe Leu Pro Val Pro  Glu Tyr Ile Asn Gln  Ser
            1085                1090                1095
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gtt ccc aaa agg  ccc gct ggc tct gtg  cag aat cct gtc tat  cac      3579
Val Pro Lys Arg  Pro Ala Gly Ser Val  Gln Asn Pro Val Tyr  His
            1100                 1105                 1110

aat cag cct ctg  aac ccc gcg ccc agc  aga gac cca cac tac  cag      3624
Asn Gln Pro Leu  Asn Pro Ala Pro Ser  Arg Asp Pro His Tyr  Gln
            1115                 1120                 1125

gac ccc cac agc  act gca gtg ggc aac  ccc gag tat ctc aac  act      3669
Asp Pro His Ser  Thr Ala Val Gly Asn  Pro Glu Tyr Leu Asn  Thr
            1130                 1135                 1140

gtc cag ccc acc  tgt gtc aac agc aca  ttc gac agc cct gcc  cac      3714
Val Gln Pro Thr  Cys Val Asn Ser Thr  Phe Asp Ser Pro Ala  His
            1145                 1150                 1155

tgg gcc cag aaa  ggc agc cac caa att  agc ctg gac aac cct  gac      3759
Trp Ala Gln Lys  Gly Ser His Gln Ile  Ser Leu Asp Asn Pro  Asp
            1160                 1165                 1170

tac cag cag gac  ttc ttt ccc aag gaa  gcc aag cca aat ggc  atc      3804
Tyr Gln Gln Asp  Phe Phe Pro Lys Glu  Ala Lys Pro Asn Gly  Ile
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ttt aag ggc tcc  aca gct gaa aat gca  gaa tac cta agg gtc  gcg      3849
Phe Lys Gly Ser  Thr Ala Glu Asn Ala  Glu Tyr Leu Arg Val  Ala
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cca caa agc agt  gaa ttt att gga gca  tga ccacggagga tagtatgagc     3899
Pro Gln Ser Ser  Glu Phe Ile Gly Ala
            1205                 1210

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cagccatgcc cgcattagct cttagaccca cagactggtt ttgcaacgtt tacaccgact   4019

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ggagcacaag ccacaagtct tccagaggat gcttgattcc agtggttctg cttcaaggct   4379

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actgtatcaa gtcatggcag gtacagtagg ataagccact ctgtcccttc ctgggcaaag   4499

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acttactccc cactgatgga ccagtggttt ccagtcatga gcgttagact gacttgtttg   4619

tcttccattc cattgttttg aaactcagta tgctgcccct gtcttgctgt catgaaatca   4679

gcaagagagg atgacacatc aaataataac tcggattcca gcccacattg gattcatcag   4739
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catttggacc aatagcccac agctgagaat gtggaatacc taaggatagc accgcttttg 4799

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actatattca tttccactct aaaaaaaaaa aaaaaaa 5616

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35 40 45

Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
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Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys
65 70 75 80

Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
85 90 95

Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
100 105 110

Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
115 120 125

Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
130 135 140

His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
145 150 155 160

Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
165 170 175

Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
180 185 190

Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
195 200 205

Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
210 215 220

Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
225 230 235 240

Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
245 250 255

Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
260 265 270

Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
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Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
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Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
305 310 315 320

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Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val
                325                 330                 335

Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
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Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
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Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr
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Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu
385                 390                 395                 400

Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
                405                 410                 415

Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln
            420                 425                 430

His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
        435                 440                 445

Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
    450                 455                 460

Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
465                 470                 475                 480

Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
                485                 490                 495

Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
            500                 505                 510

Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
        515                 520                 525

Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
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Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro
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Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
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Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
580 585 590

Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
595 600 605

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
610 615 620

Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
625 630 635 640

Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
645 650 655

Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
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Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
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Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
690 695 700

Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
705 710 715 720

Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
725 730 735

Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
740 745 750

Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
755 760 765

Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
770 775 780

Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp

785 790 795 800

Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
805 810 815

Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
820 825 830

Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro
835 840 845

Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala
850 855 860

Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
865 870 875 880

Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
885 890 895

Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
900 905 910

Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
915 920 925

Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
930 935 940

Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
945 950 955 960

Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
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Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
980 985 990

Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
995 1000 1005

Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe
1010 1015 1020

Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu
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Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn
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Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg
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Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
1070 1075 1080

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro
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Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
1100 1105 1110

Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro
1115 1120 1125

His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln
1130 1135 1140

Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala
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Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln
1160 1165 1170

Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys
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gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgagc tcttcgggga 240

gcagcg atg cga ccc tcc ggg acg gcc ggg gca gtg gat gtg aac ccc 288
Met Arg Pro Ser Gly Thr Ala Gly Ala Val Asp Val Asn Pro
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gag ggc aaa tac agc ttt ggt gcc acc tgc gtg aag aag tgt ccc cgt 336
Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg
15 20 25 30

aat tat gtg gtg aca gat cac ggc tcg tgc gtc cga gcc tgt ggg gcc 384
Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala
35 40 45

gac agc tat gag atg gag gaa gac ggc gtc cgc aag tgt aag aag tgc 432
Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys
50 55 60

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Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe
65 70 75

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Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn
80 85 90

tgc acc tcc atc agt ggc gat ctc cac atc ctg ccg gtg gca ttt agg 576
Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg
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ggt gac tcc ttc aca cat act cct cct ctg gat cca cag gaa ctg gat 624
Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp
115 120 125

att ctg aaa acc gta aag gaa atc aca ggg ttt ttg ctg att cag gct 672
Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala
130 135 140

tgg cct gaa aac agg acg gac ctc cat gcc ttt gag aac cta gaa atc 720
Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile
145 150 155

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Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val
160 165 170

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Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser
175                 180                 185                 190

gat gga gat gtg ata att tca gga aac aaa aat ttg tgc tat gca aat      864
Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn
                195                 200                 205

aca ata aac tgg aaa aaa ctg ttt ggg acc tcc ggt cag aaa acc aaa      912
Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys
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Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val
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Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg
    240                 245                 250

gac tgc gtc tct tgc cgg aat gtc agc cga ggc agg gaa tgc gtg gac     1056
Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp
255                 260                 265                 270

aag tgc aac ctt ctg gag ggt gag cca agg gag ttt gtg gag aac tct     1104
Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser
                275                 280                 285

gag tgc ata cag tgc cac cca gag tgc ctg cct cag gcc atg aac atc     1152
Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile
            290                 295                 300

acc tgc aca gga cgg gga cca gac aac tgt atc cag tgt gcc cac tac     1200
Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr
        305                 310                 315

att gac ggc ccc cac tgc gtc aag acc tgc ccg gca gga gtc atg gga     1248
Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly
    320                 325                 330

gaa aac aac acc ctg gtc tgg aag tac gca gac gcc ggc cat gtg tgc     1296
Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys
335                 340                 345                 350

cac ctg tgc cat cca aac tgc acc tac gga tgc act ggg cca ggt ctt     1344
His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu
                355                 360                 365

gaa ggc tgt cca acg aat ggg cct aag atc ccg tcc atc gcc act ggg     1392
Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly
            370                 375                 380

atg gtg ggg gcc ctc ctc ttg ctg ctg gtg gtg gcc ctg ggg atc ggc     1440
Met Val Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly
        385                 390                 395

ctc ttc atg cga agg cgc cac atc gtt cgg aag cgc acg ctg cgg agg     1488
Leu Phe Met Arg Arg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg
    400                 405                 410
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ctg ctg cag gag agg gag ctt gtg gag cct ctt aca ccc agt gga gaa     1536
Leu Leu Gln Glu Arg Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu
415                 420                 425                 430

gct ccc aac caa gct ctc ttg agg atc ttg aag gaa act gaa ttc aaa     1584
Ala Pro Asn Gln Ala Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys
                435                 440                 445

aag atc aaa gtg ctg ggc tcc ggt gcg ttc ggc acg gtg tat aag gga     1632
Lys Ile Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly
            450                 455                 460

ctc tgg atc cca gaa ggt gag aaa gtt aaa att ccc gtc gct atc aag     1680
Leu Trp Ile Pro Glu Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys
        465                 470                 475

gaa tta aga gaa gca aca tct ccg aaa gcc aac aag gaa atc ctc gat     1728
Glu Leu Arg Glu Ala Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp
    480                 485                 490

gaa gcc tac gtg atg gcc agc gtg gac aac ccc cac gtg tgc cgc ctg     1776
Glu Ala Tyr Val Met Ala Ser Val Asp Asn Pro His Val Cys Arg Leu
495                 500                 505                 510

ctg ggc atc tgc ctc acc tcc acc gtg cag ctc atc acg cag ctc atg     1824
Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met
                515                 520                 525

ccc ttc ggc tgc ctc ctg gac tat gtc cgg gaa cac aaa gac aat att     1872
Pro Phe Gly Cys Leu Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile
            530                 535                 540

ggc tcc cag tac ctg ctc aac tgg tgt gtg cag atc gca aag ggc atg     1920
Gly Ser Gln Tyr Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met
        545                 550                 555

aac tac ttg gag gac cgt cgc ttg gtg cac cgc gac ctg gca gcc agg     1968
Asn Tyr Leu Glu Asp Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg
    560                 565                 570

aac gta ctg gtg aaa aca ccg cag cat gtc aag atc aca gat ttt ggg     2016
Asn Val Leu Val Lys Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly
575                 580                 585                 590

ctg gcc aaa ctg ctg ggt gcg gaa gag aaa gaa tac cat gca gaa gga     2064
Leu Ala Lys Leu Leu Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly
                595                 600                 605

ggc aaa gtg cct atc aag tgg atg gca ttg gaa tca att tta cac aga     2112
Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg
            610                 615                 620

atc tat acc cac cag agt gat gtc tgg agc tac ggg gtg acc gtt tgg     2160
Ile Tyr Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp
        625                 630                 635

gag ttg atg acc ttt gga tcc aag cca tat gac gga atc cct gcc agc     2208
Glu Leu Met Thr Phe Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser
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    640                 645                 650

gag atc tcc tcc atc ctg gag aaa gga gaa cgc ctc cct cag cca ccc     2256
Glu Ile Ser Ser Ile Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro
655                 660                 665                 670

ata tgt acc atc gat gtc tac atg atc atg gtc aag tgc tgg atg ata     2304
Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile
                675                 680                 685

gac gca gat agt cgc cca aag ttc cgt gag ttg atc atc gaa ttc tcc     2352
Asp Ala Asp Ser Arg Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser
            690                 695                 700

aaa atg gcc cga gac ccc cag cgc tac ctt gtc att cag ggg gat gaa     2400
Lys Met Ala Arg Asp Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu
        705                 710                 715

aga atg cat ttg cca agt cct aca gac tcc aac ttc tac cgt gcc ctg     2448
Arg Met His Leu Pro Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu
    720                 725                 730

atg gat gaa gaa gac atg gac gac gtg gtg gat gcc gac gag tac ctc     2496
Met Asp Glu Glu Asp Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu
735                 740                 745                 750

atc cca cag cag ggc ttc ttc agc agc ccc tcc acg tca cgg act ccc     2544
Ile Pro Gln Gln Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro
                755                 760                 765

ctc ctg agc tct ctg agt gca acc agc aac aat tcc acc gtg gct tgc     2592
Leu Leu Ser Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys
            770                 775                 780

att gat aga aat ggg ctg caa agc tgt ccc atc aag gaa gac agc ttc     2640
Ile Asp Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe
        785                 790                 795

ttg cag cga tac agc tca gac ccc aca ggc gcc ttg act gag gac agc     2688
Leu Gln Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser
    800                 805                 810

ata gac gac acc ttc ctc cca gtg cct gaa tac ata aac cag tcc gtt     2736
Ile Asp Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val
815                 820                 825                 830

ccc aaa agg ccc gct ggc tct gtg cag aat cct gtc tat cac aat cag     2784
Pro Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
                835                 840                 845

cct ctg aac ccc gcg ccc agc aga gac cca cac tac cag gac ccc cac     2832
Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His
            850                 855                 860

agc act gca gtg ggc aac ccc gag tat ctc aac act gtc cag ccc acc     2880
Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr
        865                 870                 875

tgt gtc aac agc aca ttc gac agc cct gcc cac tgg gcc cag aaa ggc     2928
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Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala Gln Lys Gly
    880                 885                 890

agc cac caa att agc ctg gac aac cct gac tac cag cag gac ttc ttt     2976
Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln Gln Asp Phe Phe
895                 900                 905                 910

ccc aag gaa gcc aag cca aat ggc atc ttt aag ggc tcc aca gct gaa     3024
Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys Gly Ser Thr Ala Glu
                915                 920                 925

aat gca gaa tac cta agg gtc gcg cca caa agc agt gaa ttt att gga     3072
Asn Ala Glu Tyr Leu Arg Val Ala Pro Gln Ser Ser Glu Phe Ile Gly
            930                 935                 940

gca tga ccacggagga tagtatgagc cctaaaaatc cagactcttt cgatacccag      3128
Ala

gaccaagcca cagcaggtcc tccatcccaa cagccatgcc cgcattagct cttagaccca   3188

cagactggtt ttgcaacgtt tacaccgact agccaggaag tacttccacc tcgggcacat   3248

tttgggaagt tgcattcctt tgtcttcaaa ctgtgaagca tttacagaaa cgcatccagc   3308

aagaatattg tccctttgag cagaaattta tctttcaaag aggtatattt gaaaaaaaaa   3368

aaaagtatat gtgaggattt ttattgattg gggatcttgg agtttttcat tgtcgctatt   3428

gatttttact tcaatgggct cttccaacaa ggaagaagct tgctggtagc acttgctacc   3488

ctgagttcat ccaggcccaa ctgtgagcaa ggagcacaag ccacaagtct tccagaggat   3548

gcttgattcc agtggttctg cttcaaggct tccactgcaa aacactaaag atccaagaag   3608

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gacttacttt tgtaaaaatg tccccacggt acttactccc cactgatgga ccagtggttt   3788

ccagtcatga gcgttagact gacttgtttg tcttccattc cattgttttg aaactcagta   3848

tgctgcccct gtcttgctgt catgaaatca gcaagagagg atgacacatc aaataataac   3908

tcggattcca gcccacattg gattcatcag catttggacc aatagcccac agctgagaat   3968

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gctcagatga aatgcatcag gtcctttggg gcatagatca gaagactaca aaaatgaagc   4088

tgctctgaaa tctcctttag ccatcacccc aaccccccaa aattagtttg tgttacttat   4148

ggaagatagt tttctccttt tacttcactt caaaagcttt ttactcaaag agtatatgtt   4208

ccctccaggt cagctgcccc caaacccccc ccttacgctt tgtcacacaa aaagtgtctc   4268

tgccttgagt catctattca agcacttaca gctctggcca caacagggca ttttacaggt   4328
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gcgaatgaca gtagcattat gagtagtgtg gaattcaggt agtaaatatg aaactagggt 4388

ttgaaattga taatgctttc acaacatttg cagatgtttt agaaggaaaa aagttccttc 4448

ctaaaataat ttctctacaa ttggaagatt ggaagattca gctagttagg agcccacctt 4508

ttttcctaat ctgtgtgtgc cctgtaacct gactggttaa cagcagtcct ttgtaaacag 4568

tgttttaaac tctcctagtc aatatccacc ccatccaatt tatcaaggaa gaaatggttc 4628

agaaaatatt ttcagcctac agttatgttc agtcacacac acatacaaaa tgttcctttt 4688

gcttttaaag taatttttga ctcccagatc agtcagagcc cctacagcat tgttaagaaa 4748

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aaaaaaa 4815

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<212> PRT
<213> Homo sapiens

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Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr
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Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser
35 40 45

Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly
50 55 60

Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp
65 70 75 80

Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr
85 90 95

Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp
100 105 110

Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu
115 120 125

Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro

130 135 140

Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg
145 150 155 160

Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu
165 170 175

Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly
180 185 190

Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile
195 200 205

Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile
210 215 220

Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His
225 230 235 240

Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys
245 250 255

Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys
260 265 270

Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys
275 280 285

Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys
290 295 300

Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp
305 310 315 320

Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn
325 330 335

Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu
340 345 350

Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly
355 360 365

Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val
370 375 380

Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe
385 390 395 400

Met Arg Arg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu
405 410 415

Gln Glu Arg Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro
420 425 430

Asn Gln Ala Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile
435 440 445

Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp
450 455 460

Ile Pro Glu Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu
465 470 475 480

Arg Glu Ala Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala
485 490 495

Tyr Val Met Ala Ser Val Asp Asn Pro His Val Cys Arg Leu Leu Gly
500 505 510

Ile Cys Leu Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe
515 520 525

Gly Cys Leu Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser
530 535 540

Gln Tyr Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr
545 550 555 560

Leu Glu Asp Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn Val
565 570 575

Leu Val Lys Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala
580 585 590

Lys Leu Leu Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys
595 600 605

Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr
610 615 620

Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu
625 630 635 640

Met Thr Phe Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile
645 650 655

Ser Ser Ile Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys
660 665 670

Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ala
675 680 685

Asp Ser Arg Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met
690 695 700

Ala Arg Asp Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met
705 710 715 720

His Leu Pro Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp
725 730 735

Glu Glu Asp Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro
740 745 750

Gln Gln Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu
755 760 765

Ser Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp
770 775 780

Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln
785 790 795 800

Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
805 810 815

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys
820 825 830

Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu
835 840 845

Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr
850 855 860

Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val
865 870 875 880

Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala Gln Lys Gly Ser His
885 890 895

Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys
900 905 910

Glu Ala Lys Pro Asn Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala
915 920 925

Glu Tyr Leu Arg Val Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala
930 935 940

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<212> DNA
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cccggccccc acccctcgca gcaccccgcg ccccgcgccc tcccagccgg gtccagccgg 120

agccatgggg ccggagccgc agtgagcacc atg gag ctg gcg gcc ttg tgc cgc 174
Met Glu Leu Ala Ala Leu Cys Arg
1 5

tgg ggg ctc ctc ctc gcc ctc ttg ccc ccc gga gcc gcg agc acc caa 222
Trp Gly Leu Leu Leu Ala Leu Leu Pro Pro Gly Ala Ala Ser Thr Gln
10 15 20

gtg tgc acc ggc aca gac atg aag ctg cgg ctc cct gcc agt ccc gag 270
Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser Pro Glu
25 30 35 40

acc cac ctg gac atg ctc cgc cac ctc tac cag ggc tgc cag gtg gtg 318
Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln Val Val
45 50 55

cag gga aac ctg gaa ctc acc tac ctg ccc acc aat gcc agc ctg tcc 366

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Gln Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser Leu Ser
            60                  65                  70

ttc ctg cag gat atc cag gag gtg cag ggc tac gtg ctc atc gct cac      414
Phe Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile Ala His
        75                  80                  85

aac caa gtg agg cag gtc cca ctg cag agg ctg cgg att gtg cga ggc      462
Asn Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val Arg Gly
    90                  95                  100

acc cag ctc ttt gag gac aac tat gcc ctg gcc gtg cta gac aat gga      510
Thr Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp Asn Gly
105                 110                 115                 120

gac ccg ctg aac aat acc acc cct gtc aca ggg gcc tcc cca gga ggc      558
Asp Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro Gly Gly
                125                 130                 135

ctg cgg gag ctg cag ctt cga agc ctc aca gag atc ttg aaa gga ggg      606
Leu Arg Glu Leu Gln Leu Arg Ser Leu Thr Glu Ile Leu Lys Gly Gly
            140                 145                 150

gtc ttg atc cag cgg aac ccc cag ctc tgc tac cag gac acg att ttg      654
Val Leu Ile Gln Arg Asn Pro Gln Leu Cys Tyr Gln Asp Thr Ile Leu
        155                 160                 165

tgg aag gac atc ttc cac aag aac aac cag ctg gct ctc aca ctg ata      702
Trp Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr Leu Ile
    170                 175                 180

gac acc aac cgc tct cgg gcc tgc cac ccc tgt tct ccg atg tgt aag      750
Asp Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Met Cys Lys
185                 190                 195                 200

ggc tcc cgc tgc tgg gga gag agt tct gag gat tgt cag agc ctg acg      798
Gly Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser Leu Thr
                205                 210                 215

cgc act gtc tgt gcc ggt ggc tgt gcc cgc tgc aag ggg cca ctg ccc      846
Arg Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro Leu Pro
            220                 225                 230

act gac tgc tgc cat gag cag tgt gct gcc ggc tgc acg ggc ccc aag      894
Thr Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly Pro Lys
        235                 240                 245

cac tct gac tgc ctg gcc tgc ctc cac ttc aac cac agt ggc atc tgt      942
His Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly Ile Cys
    250                 255                 260

gag ctg cac tgc cca gcc ctg gtc acc tac aac aca gac acg ttt gag      990
Glu Leu His Cys Pro Ala Leu Val Thr Tyr Asn Thr Asp Thr Phe Glu
265                 270                 275                 280

tcc atg ccc aat ccc gag ggc cgg tat aca ttc ggc gcc agc tgt gtg     1038
Ser Met Pro Asn Pro Glu Gly Arg Tyr Thr Phe Gly Ala Ser Cys Val
                285                 290                 295
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act gcc tgt ccc tac aac tac ctt tct acg gac gtg gga tcc tgc acc     1086
Thr Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser Cys Thr
            300                 305                 310

ctc gtc tgc ccc ctg cac aac caa gag gtg aca gca gag gat gga aca     1134
Leu Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp Gly Thr
        315                 320                 325

cag cgg tgt gag aag tgc agc aag ccc tgt gcc cga gtg tgc tat ggt     1182
Gln Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys Tyr Gly
    330                 335                 340

ctg ggc atg gag cac ttg cga gag gtg agg gca gtt acc agt gcc aat     1230
Leu Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser Ala Asn
345                 350                 355                 360

atc cag gag ttt gct ggc tgc aag aag atc ttt ggg agc ctg gca ttt     1278
Ile Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu Ala Phe
                365                 370                 375

ctg ccg gag agc ttt gat ggg gac cca gcc tcc aac act gcc ccg ctc     1326
Leu Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala Pro Leu
            380                 385                 390

cag cca gag cag ctc caa gtg ttt gag act ctg gaa gag atc aca ggt     1374
Gln Pro Glu Gln Leu Gln Val Phe Glu Thr Leu Glu Glu Ile Thr Gly
        395                 400                 405

tac cta tac atc tca gca tgg ccg gac agc ctg cct gac ctc agc gtc     1422
Tyr Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu Ser Val
    410                 415                 420

ttc cag aac ctg caa gta atc cgg gga cga att ctg cac aat ggc gcc     1470
Phe Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn Gly Ala
425                 430                 435                 440

tac tcg ctg acc ctg caa ggg ctg ggc atc agc tgg ctg ggg ctg cgc     1518
Tyr Ser Leu Thr Leu Gln Gly Leu Gly Ile Ser Trp Leu Gly Leu Arg
                445                 450                 455

tca ctg agg gaa ctg ggc agt gga ctg gcc ctc atc cac cat aac acc     1566
Ser Leu Arg Glu Leu Gly Ser Gly Leu Ala Leu Ile His His Asn Thr
            460                 465                 470

cac ctc tgc ttc gtg cac acg gtg ccc tgg gac cag ctc ttt cgg aac     1614
His Leu Cys Phe Val His Thr Val Pro Trp Asp Gln Leu Phe Arg Asn
        475                 480                 485

ccg cac caa gct ctg ctc cac act gcc aac cgg cca gag gac gag tgt     1662
Pro His Gln Ala Leu Leu His Thr Ala Asn Arg Pro Glu Asp Glu Cys
    490                 495                 500

gtg ggc gag ggc ctg gcc tgc cac cag ctg tgc gcc cga ggg cac tgc     1710
Val Gly Glu Gly Leu Ala Cys His Gln Leu Cys Ala Arg Gly His Cys
505                 510                 515                 520

tgg ggt cca ggg ccc acc cag tgt gtc aac tgc agc cag ttc ctt cgg     1758
Trp Gly Pro Gly Pro Thr Gln Cys Val Asn Cys Ser Gln Phe Leu Arg
                525                 530                 535
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ggc cag gag tgc gtg gag gaa tgc cga gta ctg cag ggg ctc ccc agg      1806
Gly Gln Glu Cys Val Glu Glu Cys Arg Val Leu Gln Gly Leu Pro Arg
            540                 545                 550

gag tat gtg aat gcc agg cac tgt ttg ccg tgc cac cct gag tgt cag      1854
Glu Tyr Val Asn Ala Arg His Cys Leu Pro Cys His Pro Glu Cys Gln
        555                 560                 565

ccc cag aat ggc tca gtg acc tgt ttt gga ccg gag gct gac cag tgt      1902
Pro Gln Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp Gln Cys
    570                 575                 580

gtg gcc tgt gcc cac tat aag gac cct ccc ttc tgc gtg gcc cgc tgc      1950
Val Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala Arg Cys
585                 590                 595                 600

ccc agc ggt gtg aaa cct gac ctc tcc tac atg ccc atc tgg aag ttt      1998
Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp Lys Phe
                605                 610                 615

cca gat gag gag ggc gca tgc cag cct tgc ccc atc aac tgc acc cac      2046
Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn Cys Thr His
            620                 625                 630

tcc tgt gtg gac ctg gat gac aag ggc tgc ccc gcc gag cag aga gcc      2094
Ser Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu Gln Arg Ala
        635                 640                 645

agc cct ctg acg tcc atc gtc tct gcg gtg gtt ggc att ctg ctg gtc      2142
Ser Pro Leu Thr Ser Ile Val Ser Ala Val Val Gly Ile Leu Leu Val
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gtg gtc ttg ggg gtg gtc ttt ggg atc ctc atc aag cga cgg cag cag      2190
Val Val Leu Gly Val Val Phe Gly Ile Leu Ile Lys Arg Arg Gln Gln
665                 670                 675                 680

aag atc cgg aag tac acg atg cgg aga ctg ctg cag gaa acg gag ctg      2238
Lys Ile Arg Lys Tyr Thr Met Arg Arg Leu Leu Gln Glu Thr Glu Leu
                685                 690                 695

gtg gag ccg ctg aca cct agc gga gcg atg ccc aac cag gcg cag atg      2286
Val Glu Pro Leu Thr Pro Ser Gly Ala Met Pro Asn Gln Ala Gln Met
            700                 705                 710

cgg atc ctg aaa gag acg gag ctg agg aag gtg aag gtg ctt gga tct      2334
Arg Ile Leu Lys Glu Thr Glu Leu Arg Lys Val Lys Val Leu Gly Ser
        715                 720                 725

ggc gct ttt ggc aca gtc tac aag ggc atc tgg atc cct gat ggg gag      2382
Gly Ala Phe Gly Thr Val Tyr Lys Gly Ile Trp Ile Pro Asp Gly Glu
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aat gtg aaa att cca gtg gcc atc aaa gtg ttg agg gaa aac aca tcc      2430
Asn Val Lys Ile Pro Val Ala Ile Lys Val Leu Arg Glu Asn Thr Ser
745                 750                 755                 760

ccc aaa gcc aac aaa gaa atc tta gac gaa gca tac gtg atg gct ggt      2478
Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Gly
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gtg ggc tcc cca tat gtc tcc cgc ctt ctg ggc atc tgc ctg aca tcc 2526
Val Gly Ser Pro Tyr Val Ser Arg Leu Leu Gly Ile Cys Leu Thr Ser
780 785 790

acg gtg cag ctg gtg aca cag ctt atg ccc tat ggc tgc ctc tta gac 2574
Thr Val Gln Leu Val Thr Gln Leu Met Pro Tyr Gly Cys Leu Leu Asp
795 800 805

cat gtc cgg gaa aac cgc gga cgc ctg ggc tcc cag gac ctg ctg aac 2622
His Val Arg Glu Asn Arg Gly Arg Leu Gly Ser Gln Asp Leu Leu Asn
810 815 820

tgg tgt atg cag att gcc aag ggg atg agc tac ctg gag gat gtg cgg 2670
Trp Cys Met Gln Ile Ala Lys Gly Met Ser Tyr Leu Glu Asp Val Arg
825 830 835 840

ctc gta cac agg gac ttg gcc gct cgg aac gtg ctg gtc aag agt ccc 2718
Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Ser Pro
845 850 855

aac cat gtc aaa att aca gac ttc ggg ctg gct cgg ctg ctg gac att 2766
Asn His Val Lys Ile Thr Asp Phe Gly Leu Ala Arg Leu Leu Asp Ile
860 865 870

gac gag aca gag tac cat gca gat ggg ggc aag gtg ccc atc aag tgg 2814
Asp Glu Thr Glu Tyr His Ala Asp Gly Gly Lys Val Pro Ile Lys Trp
875 880 885

atg gcg ctg gag tcc att ctc cgc cgg cgg ttc acc cac cag agt gat 2862
Met Ala Leu Glu Ser Ile Leu Arg Arg Arg Phe Thr His Gln Ser Asp
890 895 900

gtg tgg agt tat ggt gtg act gtg tgg gag ctg atg act ttt ggg gcc 2910
Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala
905 910 915 920

aaa cct tac gat ggg atc cca gcc cgg gag atc cct gac ctg ctg gaa 2958
Lys Pro Tyr Asp Gly Ile Pro Ala Arg Glu Ile Pro Asp Leu Leu Glu
925 930 935

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Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
940 945 950

atg atc atg gtc aaa tgt tgg atg att gac tct gaa tgt cgg cca aga 3054
Met Ile Met Val Lys Cys Trp Met Ile Asp Ser Glu Cys Arg Pro Arg
955 960 965

ttc cgg gag ttg gtg tct gaa ttc tcc cgc atg gcc agg gac ccc cag 3102
Phe Arg Glu Leu Val Ser Glu Phe Ser Arg Met Ala Arg Asp Pro Gln
970 975 980

cgc ttt gtg gtc atc cag aat gag gac ttg ggc cca gcc agt ccc ttg 3150
Arg Phe Val Val Ile Gln Asn Glu Asp Leu Gly Pro Ala Ser Pro Leu
985 990 995 1000

gac agc acc ttc tac cgc tca ctg ctg gag gac gat gac atg ggg 3195

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Asp Ser Thr Phe Tyr  Arg Ser Leu Leu Glu  Asp Asp Asp Met Gly
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gac ctg gtg gat gct  gag gag tat ctg gta  ccc cag cag ggc ttc      3240
Asp Leu Val Asp Ala  Glu Glu Tyr Leu Val  Pro Gln Gln Gly Phe
                1020                1025                1030

ttc tgt cca gac cct  gcc ccg ggc gct ggg  ggc atg gtc cac cac      3285
Phe Cys Pro Asp Pro  Ala Pro Gly Ala Gly  Gly Met Val His His
                1035                1040                1045

agg cac cgc agc tca  tct acc agg agt ggc  ggt ggg gac ctg aca      3330
Arg His Arg Ser Ser  Ser Thr Arg Ser Gly  Gly Gly Asp Leu Thr
                1050                1055                1060

cta ggg ctg gag ccc  tct gaa gag gag gcc  ccc agg tct cca ctg      3375
Leu Gly Leu Glu Pro  Ser Glu Glu Glu Ala  Pro Arg Ser Pro Leu
                1065                1070                1075

gca ccc tcc gaa ggg  gct ggc tcc gat gta  ttt gat ggt gac ctg      3420
Ala Pro Ser Glu Gly  Ala Gly Ser Asp Val  Phe Asp Gly Asp Leu
                1080                1085                1090

gga atg ggg gca gcc  aag ggg ctg caa agc  ctc ccc aca cat gac      3465
Gly Met Gly Ala Ala  Lys Gly Leu Gln Ser  Leu Pro Thr His Asp
                1095                1100                1105

ccc agc cct cta cag  cgg tac agt gag gac  ccc aca gta ccc ctg      3510
Pro Ser Pro Leu Gln  Arg Tyr Ser Glu Asp  Pro Thr Val Pro Leu
                1110                1115                1120

ccc tct gag act gat  ggc tac gtt gcc ccc  ctg acc tgc agc ccc      3555
Pro Ser Glu Thr Asp  Gly Tyr Val Ala Pro  Leu Thr Cys Ser Pro
                1125                1130                1135

cag cct gaa tat gtg  aac cag cca gat gtt  cgg ccc cag ccc cct      3600
Gln Pro Glu Tyr Val  Asn Gln Pro Asp Val  Arg Pro Gln Pro Pro
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tcg ccc cga gag ggc  cct ctg cct gct gcc  cga cct gct ggt gcc      3645
Ser Pro Arg Glu Gly  Pro Leu Pro Ala Ala  Arg Pro Ala Gly Ala
                1155                1160                1165

act ctg gaa agg gcc  aag act ctc tcc cca  ggg aag aat ggg gtc      3690
Thr Leu Glu Arg Ala  Lys Thr Leu Ser Pro  Gly Lys Asn Gly Val
                1170                1175                1180

gtc aaa gac gtt ttt  gcc ttt ggg ggt gcc  gtg gag aac ccc gag      3735
Val Lys Asp Val Phe  Ala Phe Gly Gly Ala  Val Glu Asn Pro Glu
                1185                1190                1195

tac ttg aca ccc cag  gga gga gct gcc cct  cag ccc cac cct cct      3780
Tyr Leu Thr Pro Gln  Gly Gly Ala Ala Pro  Gln Pro His Pro Pro
                1200                1205                1210

cct gcc ttc agc cca  gcc ttc gac aac ctc  tat tac tgg gac cag      3825
Pro Ala Phe Ser Pro  Ala Phe Asp Asn Leu  Tyr Tyr Trp Asp Gln
                1215                1220                1225
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gac cca cca gag cgg ggg gct cca ccc agc acc ttc aaa ggg aca 3870
Asp Pro Pro Glu Arg Gly Ala Pro Pro Ser Thr Phe Lys Gly Thr
1230 1235 1240

cct acg gca gag aac cca gag tac ctg ggt ctg gac gtg cca gtg 3915
Pro Thr Ala Glu Asn Pro Glu Tyr Leu Gly Leu Asp Val Pro Val
1245 1250 1255

tga accagaaggc caagtccgca gaagccctga tgtgtcctca gggagcaggg 3968

aaggcctgac ttctgctggc atcaagaggt gggagggccc tccgaccact tccaggggaa 4028

cctgccatgc caggaacctg tcctaaggaa ccttccttcc tgcttgagtt cccagatggc 4088

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35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu

85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
500 505 510

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545 550 555 560

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Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
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Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
            580                 585                 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
        595                 600                 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
    610                 615                 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625                 630                 635                 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser
                645                 650                 655

Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly
            660                 665                 670

Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
        675                 680                 685

Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly
    690                 695                 700

Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
705                 710                 715                 720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
                725                 730                 735

Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile
            740                 745                 750

Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
        755                 760                 765

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
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Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
785                 790                 795                 800
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Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg
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Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
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Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala
        835                 840                 845

Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
    850                 855                 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
865                 870                 875                 880

Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg
                885                 890                 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
            900                 905                 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala
        915                 920                 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro
    930                 935                 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
945                 950                 955                 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe
                965                 970                 975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu
            980                 985                 990

Asp Leu Gly Pro Ala Ser Pro Leu  Asp Ser Thr Phe Tyr  Arg Ser Leu
        995                 1000                1005

Leu Glu  Asp Asp Asp Met Gly  Asp Leu Val Asp Ala  Glu Glu Tyr
    1010                1015                1020

Leu Val  Pro Gln Gln Gly Phe  Phe Cys Pro Asp Pro  Ala Pro Gly
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Ala Gly Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg
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Ser Gly Gly Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu
1055 1060 1065

Glu Ala Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser
1070 1075 1080

Asp Val Phe Asp Gly Asp Leu Gly Met Gly Ala Ala Lys Gly Leu
1085 1090 1095

Gln Ser Leu Pro Thr His Asp Pro Ser Pro Leu Gln Arg Tyr Ser
1100 1105 1110

Glu Asp Pro Thr Val Pro Leu Pro Ser Glu Thr Asp Gly Tyr Val
1115 1120 1125

Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val Asn Gln Pro
1130 1135 1140

Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro Leu Pro
1145 1150 1155

Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Ala Lys Thr Leu
1160 1165 1170

Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val Phe Ala Phe Gly
1175 1180 1185

Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln Gly Gly Ala
1190 1195 1200

Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala Phe Asp
1205 1210 1215

Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala Pro
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Leu Gly Leu Asp Val Pro Val
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gtggctcttg cctcgatgtc ctagcctagg ggcccccggg ccggacttgg ctgggctccc 180

ttcaccctct gcggagtc atg agg gcg aac gac gct ctg cag gtg ctg ggc 231
Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly
1 5 10

ttg ctt ttc agc ctg gcc cgg ggc tcc gag gtg ggc aac tct cag gca 279
Leu Leu Phe Ser Leu Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala
15 20 25

gtg tgt cct ggg act ctg aat ggc ctg agt gtg acc ggc gat gct gag 327
Val Cys Pro Gly Thr Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu
30 35 40

aac caa tac cag aca ctg tac aag ctc tac gag agg tgt gag gtg gtg 375
Asn Gln Tyr Gln Thr Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val
45 50 55

atg ggg aac ctt gag att gtg ctc acg gga cac aat gcc gac ctc tcc 423
Met Gly Asn Leu Glu Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser
60 65 70 75

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Phe Leu Gln Trp Ile Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met
80 85 90

aat gaa ttc tct act cta cca ttg ccc aac ctc cgc gtg gtg cga ggg 519
Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly
95 100 105

acc cag gtc tac gat ggg aag ttt gcc atc ttc gtc atg ttg aac tat 567
Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr
110 115 120

aac acc aac tcc agc cac gct ctg cgc cag ctc cgc ttg act cag ctc 615
Asn Thr Asn Ser Ser His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu
125 130 135

acc gag att ctg tca ggg ggt gtt tat att gag aag aac gat aag ctt 663
Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu

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140                 145                 150                 155

tgt cac atg gac aca att gac tgg agg gac atc gtg agg gac cga gat      711
Cys His Met Asp Thr Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp
                160                 165                 170

gct gag ata gtg gtg aag gac aat ggc aga agc tgt ccc ccc tgt cat      759
Ala Glu Ile Val Val Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His
            175                 180                 185

gag gtt tgc aag ggg cga tgc tgg ggt cct gga tca gaa gac tgc cag      807
Glu Val Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln
        190                 195                 200

aca ttg acc aag acc atc tgt gct cct cag tgt aat ggt cac tgc ttt      855
Thr Leu Thr Lys Thr Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe
    205                 210                 215

ggg ccc aac ccc aac cag tgc tgc cat gat gag tgt gcc ggg ggc tgc      903
Gly Pro Asn Pro Asn Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys
220                 225                 230                 235

tca ggc cct cag gac aca gac tgc ttt gcc tgc cgg cac ttc aat gac      951
Ser Gly Pro Gln Asp Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp
                240                 245                 250

agt gga gcc tgt gta cct cgc tgt cca cag cct ctt gtc tac aac aag      999
Ser Gly Ala Cys Val Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys
            255                 260                 265

cta act ttc cag ctg gaa ccc aat ccc cac acc aag tat cag tat gga     1047
Leu Thr Phe Gln Leu Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly
        270                 275                 280

gga gtt tgt gta gcc agc tgt ccc cat aac ttt gtg gtg gat caa aca     1095
Gly Val Cys Val Ala Ser Cys Pro His Asn Phe Val Val Asp Gln Thr
    285                 290                 295

tcc tgt gtc agg gcc tgt cct cct gac aag atg gaa gta gat aaa aat     1143
Ser Cys Val Arg Ala Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn
300                 305                 310                 315

ggg ctc aag atg tgt gag cct tgt ggg gga cta tgt ccc aaa gcc tgt     1191
Gly Leu Lys Met Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys
                320                 325                 330

gag gga aca ggc tct ggg agc cgc ttc cag act gtg gac tcg agc aac     1239
Glu Gly Thr Gly Ser Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn
            335                 340                 345

att gat gga ttt gtg aac tgc acc aag atc ctg ggc aac ctg gac ttt     1287
Ile Asp Gly Phe Val Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe
        350                 355                 360

ctg atc acc ggc ctc aat gga gac ccc tgg cac aag atc cct gcc ctg     1335
Leu Ile Thr Gly Leu Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu
    365                 370                 375

gac cca gag aag ctc aat gtc ttc cgg aca gta cgg gag atc aca ggt     1383
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Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly
380                 385                 390                 395

tac ctg aac atc cag tcc tgg ccg ccc cac atg cac aac ttc agt gtt     1431
Tyr Leu Asn Ile Gln Ser Trp Pro Pro His Met His Asn Phe Ser Val
                400                 405                 410

ttt tcc aat ttg aca acc att gga ggc aga agc ctc tac aac cgg ggc     1479
Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly
            415                 420                 425

ttc tca ttg ttg atc atg aag aac ttg aat gtc aca tct ctg ggc ttc     1527
Phe Ser Leu Leu Ile Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe
        430                 435                 440

cga tcc ctg aag gaa att agt gct ggg cgt atc tat ata agt gcc aat     1575
Arg Ser Leu Lys Glu Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn
    445                 450                 455

agg cag ctc tgc tac cac cac tct ttg aac tgg acc aag gtg ctt cgg     1623
Arg Gln Leu Cys Tyr His His Ser Leu Asn Trp Thr Lys Val Leu Arg
460                 465                 470                 475

ggg cct acg gaa gag cga cta gac atc aag cat aat cgg ccg cgc aga     1671
Gly Pro Thr Glu Glu Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg
                480                 485                 490

gac tgc gtg gca gag ggc aaa gtg tgt gac cca ctg tgc tcc tct ggg     1719
Asp Cys Val Ala Glu Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly
            495                 500                 505

gga tgc tgg ggc cca ggc cct ggt cag tgc ttg tcc tgt cga aat tat     1767
Gly Cys Trp Gly Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr
        510                 515                 520

agc cga gga ggt gtc tgt gtg acc cac tgc aac ttt ctg aat ggg gag     1815
Ser Arg Gly Gly Val Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu
    525                 530                 535

cct cga gaa ttt gcc cat gag gcc gaa tgc ttc tcc tgc cac ccg gaa     1863
Pro Arg Glu Phe Ala His Glu Ala Glu Cys Phe Ser Cys His Pro Glu
540                 545                 550                 555

tgc caa ccc atg ggg ggc act gcc aca tgc aat ggc tcg ggc tct gat     1911
Cys Gln Pro Met Gly Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp
                560                 565                 570

act tgt gct caa tgt gcc cat ttt cga gat ggg ccc cac tgt gtg agc     1959
Thr Cys Ala Gln Cys Ala His Phe Arg Asp Gly Pro His Cys Val Ser
            575                 580                 585

agc tgc ccc cat gga gtc cta ggt gcc aag ggc cca atc tac aag tac     2007
Ser Cys Pro His Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr
        590                 595                 600

cca gat gtt cag aat gaa tgt cgg ccc tgc cat gag aac tgc acc cag     2055
Pro Asp Val Gln Asn Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln
    605                 610                 615
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ggg tgt aaa gga cca gag ctt caa gac tgt tta gga caa aca ctg gtg     2103
Gly Cys Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val
620                 625                 630                 635

ctg atc ggc aaa acc cat ctg aca atg gct ttg aca gtg ata gca gga     2151
Leu Ile Gly Lys Thr His Leu Thr Met Ala Leu Thr Val Ile Ala Gly
                640                 645                 650

ttg gta gtg att ttc atg atg ctg ggc ggc act ttt ctc tac tgg cgt     2199
Leu Val Val Ile Phe Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg
            655                 660                 665

ggg cgc cgg att cag aat aaa agg gct atg agg cga tac ttg gaa cgg     2247
Gly Arg Arg Ile Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg
        670                 675                 680

ggt gag agc ata gag cct ctg gac ccc agt gag aag gct aac aaa gtc     2295
Gly Glu Ser Ile Glu Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val
    685                 690                 695

ttg gcc aga atc ttc aaa gag aca gag cta agg aag ctt aaa gtg ctt     2343
Leu Ala Arg Ile Phe Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu
700                 705                 710                 715

ggc tcg ggt gtc ttt gga act gtg cac aaa gga gtg tgg atc cct gag     2391
Gly Ser Gly Val Phe Gly Thr Val His Lys Gly Val Trp Ile Pro Glu
                720                 725                 730

ggt gaa tca atc aag att cca gtc tgc att aaa gtc att gag gac aag     2439
Gly Glu Ser Ile Lys Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys
            735                 740                 745

agt gga cgg cag agt ttt caa gct gtg aca gat cat atg ctg gcc att     2487
Ser Gly Arg Gln Ser Phe Gln Ala Val Thr Asp His Met Leu Ala Ile
        750                 755                 760

ggc agc ctg gac cat gcc cac att gta agg ctg ctg gga cta tgc cca     2535
Gly Ser Leu Asp His Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro
    765                 770                 775

ggg tca tct ctg cag ctt gtc act caa tat ttg cct ctg ggt tct ctg     2583
Gly Ser Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu
780                 785                 790                 795

ctg gat cat gtg aga caa cac cgg ggg gca ctg ggg cca cag ctg ctg     2631
Leu Asp His Val Arg Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu
                800                 805                 810

ctc aac tgg gga gta caa att gcc aag gga atg tac tac ctt gag gaa     2679
Leu Asn Trp Gly Val Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu
            815                 820                 825

cat ggt atg gtg cat aga aac ctg gct gcc cga aac gtg cta ctc aag     2727
His Gly Met Val His Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys
        830                 835                 840

tca ccc agt cag gtt cag gtg gca gat ttt ggt gtg gct gac ctg ctg     2775
Ser Pro Ser Gln Val Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu
    845                 850                 855
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cct cct gat gat aag cag ctg cta tac agt gag gcc aag act cca att      2823
Pro Pro Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile
860                 865                 870                 875

aag tgg atg gcc ctt gag agt atc cac ttt ggg aaa tac aca cac cag      2871
Lys Trp Met Ala Leu Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln
                880                 885                 890

agt gat gtc tgg agc tat ggt gtg aca gtt tgg gag ttg atg acc ttc      2919
Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe
            895                 900                 905

ggg gca gag ccc tat gca ggg cta cga ttg gct gaa gta cca gac ctg      2967
Gly Ala Glu Pro Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu
        910                 915                 920

cta gag aag ggg gag cgg ttg gca cag ccc cag atc tgc aca att gat      3015
Leu Glu Lys Gly Glu Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp
    925                 930                 935

gtc tac atg gtg atg gtc aag tgt tgg atg att gat gag aac att cgc      3063
Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg
940                 945                 950                 955

cca acc ttt aaa gaa cta gcc aat gag ttc acc agg atg gcc cga gac      3111
Pro Thr Phe Lys Glu Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp
                960                 965                 970

cca cca cgg tat ctg gtc ata aag aga gag agt ggg cct gga ata gcc      3159
Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala
            975                 980                 985

cct ggg cca gag ccc cat ggt ctg aca aac aag aag cta  gag gaa gta     3207
Pro Gly Pro Glu Pro His Gly Leu Thr Asn Lys Lys Leu  Glu Glu Val
        990                 995                 1000

gag ctg  gag cca gaa cta gac  cta gac cta gac ttg  gaa gca gag       3252
Glu Leu  Glu Pro Glu Leu Asp  Leu Asp Leu Asp Leu  Glu Ala Glu
    1005                1010                1015

gag gac  aac ctg gca acc acc  aca ctg ggc tcc gcc  ctc agc cta       3297
Glu Asp  Asn Leu Ala Thr Thr  Thr Leu Gly Ser Ala  Leu Ser Leu
    1020                1025                1030

cca gtt  gga aca ctt aat cgg  cca cgt ggg agc cag  agc ctt tta       3342
Pro Val  Gly Thr Leu Asn Arg  Pro Arg Gly Ser Gln  Ser Leu Leu
    1035                1040                1045

agt cca  tca tct gga tac atg  ccc atg aac cag ggt  aat ctt ggg       3387
Ser Pro  Ser Ser Gly Tyr Met  Pro Met Asn Gln Gly  Asn Leu Gly
    1050                1055                1060

ggg tct  tgc cag gag tct gca  gtt tct ggg agc agt  gaa cgg tgc       3432
Gly Ser  Cys Gln Glu Ser Ala  Val Ser Gly Ser Ser  Glu Arg Cys
    1065                1070                1075

ccc cgt  cca gtc tct cta cac  cca atg cca cgg gga  tgc ctg gca       3477
Pro Arg  Pro Val Ser Leu His  Pro Met Pro Arg Gly  Cys Leu Ala
```

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    1080                1085                1090

tca gag  tca tca gag ggg cat  gta aca ggc tct gag  gct gag ctc      3522
Ser Glu  Ser Ser Glu Gly His  Val Thr Gly Ser Glu  Ala Glu Leu
    1095                1100                1105

cag gag  aaa gtg tca atg tgt  aga agc cgg agc agg  agc cgg agc      3567
Gln Glu  Lys Val Ser Met Cys  Arg Ser Arg Ser Arg  Ser Arg Ser
    1110                1115                1120

cca cgg  cca cgc gga gat agc  gcc tac cat tcc cag  cgc cac agt      3612
Pro Arg  Pro Arg Gly Asp Ser  Ala Tyr His Ser Gln  Arg His Ser
    1125                1130                1135

ctg ctg  act cct gtt acc cca  ctc tcc cca ccc ggg  tta gag gaa      3657
Leu Leu  Thr Pro Val Thr Pro  Leu Ser Pro Pro Gly  Leu Glu Glu
    1140                1145                1150

gag gat  gtc aac ggt tat gtc  atg cca gat aca cac  ctc aaa ggt      3702
Glu Asp  Val Asn Gly Tyr Val  Met Pro Asp Thr His  Leu Lys Gly
    1155                1160                1165

act ccc  tcc tcc cgg gaa ggc  acc ctt tct tca gtg  ggt ctc agt      3747
Thr Pro  Ser Ser Arg Glu Gly  Thr Leu Ser Ser Val  Gly Leu Ser
    1170                1175                1180

tct gtc  ctg ggt act gaa gaa  gaa gat gaa gat gag  gag tat gaa      3792
Ser Val  Leu Gly Thr Glu Glu  Glu Asp Glu Asp Glu  Glu Tyr Glu
    1185                1190                1195

tac atg  aac cgg agg aga agg  cac agt cca cct cat  ccc cct agg      3837
Tyr Met  Asn Arg Arg Arg Arg  His Ser Pro Pro His  Pro Pro Arg
    1200                1205                1210

cca agt  tcc ctt gag gag ctg  ggt tat gag tac atg  gat gtg ggg      3882
Pro Ser  Ser Leu Glu Glu Leu  Gly Tyr Glu Tyr Met  Asp Val Gly
    1215                1220                1225

tca gac  ctc agt gcc tct ctg  ggc agc aca cag agt  tgc cca ctc      3927
Ser Asp  Leu Ser Ala Ser Leu  Gly Ser Thr Gln Ser  Cys Pro Leu
    1230                1235                1240

cac cct  gta ccc atc atg ccc  act gca ggc aca act  cca gat gaa      3972
His Pro  Val Pro Ile Met Pro  Thr Ala Gly Thr Thr  Pro Asp Glu
    1245                1250                1255

gac tat  gaa tat atg aat cgg  caa cga gat gga ggt  ggt cct ggg      4017
Asp Tyr  Glu Tyr Met Asn Arg  Gln Arg Asp Gly Gly  Gly Pro Gly
    1260                1265                1270

ggt gat  tat gca gcc atg ggg  gcc tgc cca gca tct  gag caa ggg      4062
Gly Asp  Tyr Ala Ala Met Gly  Ala Cys Pro Ala Ser  Glu Gln Gly
    1275                1280                1285

tat gaa  gag atg aga gct ttt  cag ggg cct gga cat  cag gcc ccc      4107
Tyr Glu  Glu Met Arg Ala Phe  Gln Gly Pro Gly His  Gln Ala Pro
    1290                1295                1300

cat gtc  cat tat gcc cgc cta  aaa act cta cgt agc  tta gag gct      4152
```

```
His Val  His Tyr Ala Arg Leu  Lys Thr Leu Arg Ser  Leu Glu Ala
    1305                 1310                 1315

aca gac  tct gcc ttt gat aac  cct gat tac tgg cat  agc agg ctt      4197
Thr Asp  Ser Ala Phe Asp Asn  Pro Asp Tyr Trp His  Ser Arg Leu
    1320                 1325                 1330

ttc ccc  aag gct aat gcc cag  aga acg taa ctcctgctcc ctgtggcact     4247
Phe Pro  Lys Ala Asn Ala Gln  Arg Thr
    1335                 1340

cagggagcat ttaatggcag ctagtgcctt tagagggtac cgtcttctcc ctattccctc   4307

tctctcccag gtcccagccc cttttcccca gtcccagaca attccattca atctttggag   4367

gcttttaaac attttgacac aaaattctta tggtatgtag ccagctgtgc actttcttct   4427

ctttcccaac cccaggaaag gttttcctta ttttgtgtgc tttcccagtc ccattcctca   4487

gcttcttcac aggcactcct ggagatatga aggattactc tccatatccc ttcctctcag   4547

gctcttgact acttggaact aggctcttat gtgtgccttt gtttcccatc agactgtcaa   4607

gaagaggaaa gggaggaaac ctagcagagg aaagtgtaat tttggtttat gactcttaac   4667

cccctagaaa gacagaagct taaaatctgt gaagaaagag gttaggagta gatattgatt   4727

actatcataa ttcagcactt aactatgagc caggcatcat actaaacttc acctacatta   4787

tctcacttag tcctttatca tccttaaaac aattctgtga catacatatt atctcatttt   4847

acacaaaggg aagtcgggca tggtggctca tgcctgtaat ctcagcactt tgggaggctg   4907

aggcagaagg attacctgag gcaaggagtt tgagaccagc ttagccaaca tagtaagacc   4967

cccatctc                                                           4975
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<210> 12
<211> 1342
<212> PRT
<213> Homo sapiens

<400> 12

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Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly Leu Leu Phe Ser Leu
1               5                  10                  15

Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr
            20                  25                  30

Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr
        35                  40                  45

Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu
    50                  55                  60
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Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile
65 70 75 80

Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr
85 90 95

Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp
100 105 110

Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser
115 120 125

His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser
130 135 140

Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr
145 150 155 160

Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val
165 170 175

Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly
180 185 190

Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr
195 200 205

Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn
210 215 220

Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp
225 230 235 240

Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val
245 250 255

Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu
260 265 270

Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala
275 280 285

Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala

290 295 300

Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys
305 310 315 320

Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser
325 330 335

Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val
340 345 350

Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu
355 360 365

Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu
370 375 380

Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly Tyr Leu Asn Ile Gln
385 390 395 400

Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr
405 410 415

Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile
420 425 430

Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe Arg Ser Leu Lys Glu
435 440 445

Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln Leu Cys Tyr
450 455 460

His His Ser Leu Asn Trp Thr Lys Val Leu Arg Gly Pro Thr Glu Glu
465 470 475 480

Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg Asp Cys Val Ala Glu
485 490 495

Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro
500 505 510

Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Gly Gly Val
515 520 525

Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu Pro Arg Glu Phe Ala
530 535 540

His Glu Ala Glu Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Gly
545 550 555 560

Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp Thr Cys Ala Gln Cys
565 570 575

Ala His Phe Arg Asp Gly Pro His Cys Val Ser Ser Cys Pro His Gly
580 585 590

Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Val Gln Asn
595 600 605

Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro
610 615 620

Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val Leu Ile Gly Lys Thr
625 630 635 640

His Leu Thr Met Ala Leu Thr Val Ile Ala Gly Leu Val Val Ile Phe
645 650 655

Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln
660 665 670

Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu
675 680 685

Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe
690 695 700

Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe
705 710 715 720

Gly Thr Val His Lys Gly Val Trp Ile Pro Glu Gly Glu Ser Ile Lys
725 730 735

Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser
740 745 750

Phe Gln Ala Val Thr Asp His Met Leu Ala Ile Gly Ser Leu Asp His
755 760 765

Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln
770 775 780

Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg
785 790 795 800

Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val
805 810 815

Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Gly Met Val His
820 825 830

Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys Ser Pro Ser Gln Val
835 840 845

Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys
850 855 860

Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu
865 870 875 880

Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser
885 890 895

Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr
900 905 910

Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu Leu Glu Lys Gly Glu
915 920 925

Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met
930 935 940

Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu
945 950 955 960

Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu
965 970 975

Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro
980 985 990

His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val Glu Leu Glu Pro Glu
995 1000 1005

Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn Leu Ala
1010 1015 1020

Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu Pro Val Gly Thr Leu
1025 1030 1035

Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser Ser Gly
1040 1045 1050

Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Gly Ser Cys Gln Glu
1055 1060 1065

Ser Ala Val Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro Val Ser
1070 1075 1080

Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu
1085 1090 1095

Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser
1100 1105 1110

Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly
1115 1120 1125

Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val
1130 1135 1140

Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly
1145 1150 1155

Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg
1160 1165 1170

Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr
1175 1180 1185

Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg
1190 1195 1200

Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu
1205 1210 1215

Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala

1220 1225 1230

Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile
1235 1240 1245

Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met
1250 1255 1260

Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala
1265 1270 1275

Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg
1280 1285 1290

Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala
1295 1300 1305

Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe
1310 1315 1320

Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn
1325 1330 1335

Ala Gln Arg Thr
1340

<210> 13
<211> 4975
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (199)..(4227)
<223> HER-3 mutant coding sequence

<220>
<221> mutation
<222> (1877)..(1877)
<223> mutation, comprising substitution of "a" instead of "g" at this position

<400> 13
ctctcacaca cacacacccc tcccctgcca tccctccccg gactccggct ccggctccga 60

ttgcaatttg caacctccgc tgccgtcgcc gcagcagcca ccaattcgcc agcggttcag 120

gtggctcttg cctcgatgtc ctagcctagg ggcccccggg ccggacttgg ctgggctccc 180

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ttcacctct gcggagtc atg agg gcg aac gac gct ctg cag gtg ctg ggc      231
                  Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly
                  1               5                   10

ttg ctt ttc agc ctg gcc cgg ggc tcc gag gtg ggc aac tct cag gca      279
Leu Leu Phe Ser Leu Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala
            15                  20                  25

gtg tgt cct ggg act ctg aat ggc ctg agt gtg acc ggc gat gct gag      327
Val Cys Pro Gly Thr Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu
        30                  35                  40

aac caa tac cag aca ctg tac aag ctc tac gag agg tgt gag gtg gtg      375
Asn Gln Tyr Gln Thr Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val
    45                  50                  55

atg ggg aac ctt gag att gtg ctc acg gga cac aat gcc gac ctc tcc      423
Met Gly Asn Leu Glu Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser
60                  65                  70                  75

ttc ctg cag tgg att cga gaa gtg aca ggc tat gtc ctc gtg gcc atg      471
Phe Leu Gln Trp Ile Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met
                80                  85                  90

aat gaa ttc tct act cta cca ttg ccc aac ctc cgc gtg gtg cga ggg      519
Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly
            95                  100                 105

acc cag gtc tac gat ggg aag ttt gcc atc ttc gtc atg ttg aac tat      567
Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr
        110                 115                 120

aac acc aac tcc agc cac gct ctg cgc cag ctc cgc ttg act cag ctc      615
Asn Thr Asn Ser Ser His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu
    125                 130                 135

acc gag att ctg tca ggg ggt gtt tat att gag aag aac gat aag ctt      663
Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu
140                 145                 150                 155

tgt cac atg gac aca att gac tgg agg gac atc gtg agg gac cga gat      711
Cys His Met Asp Thr Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp
                160                 165                 170

gct gag ata gtg gtg aag gac aat ggc aga agc tgt ccc ccc tgt cat      759
Ala Glu Ile Val Val Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His
            175                 180                 185

gag gtt tgc aag ggg cga tgc tgg ggt cct gga tca gaa gac tgc cag      807
Glu Val Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln
        190                 195                 200

aca ttg acc aag acc atc tgt gct cct cag tgt aat ggt cac tgc ttt      855
Thr Leu Thr Lys Thr Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe
    205                 210                 215

ggg ccc aac ccc aac cag tgc tgc cat gat gag tgt gcc ggg ggc tgc      903
Gly Pro Asn Pro Asn Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys
220                 225                 230                 235
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tca ggc cct cag gac aca gac tgc ttt gcc tgc cgg cac ttc aat gac      951
Ser Gly Pro Gln Asp Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp
                240                 245                 250

agt gga gcc tgt gta cct cgc tgt cca cag cct ctt gtc tac aac aag      999
Ser Gly Ala Cys Val Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys
            255                 260                 265

cta act ttc cag ctg gaa ccc aat ccc cac acc aag tat cag tat gga     1047
Leu Thr Phe Gln Leu Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly
        270                 275                 280

gga gtt tgt gta gcc agc tgt ccc cat aac ttt gtg gtg gat caa aca     1095
Gly Val Cys Val Ala Ser Cys Pro His Asn Phe Val Val Asp Gln Thr
    285                 290                 295

tcc tgt gtc agg gcc tgt cct cct gac aag atg gaa gta gat aaa aat     1143
Ser Cys Val Arg Ala Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn
300                 305                 310                 315

ggg ctc aag atg tgt gag cct tgt ggg gga cta tgt ccc aaa gcc tgt     1191
Gly Leu Lys Met Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys
                320                 325                 330

gag gga aca ggc tct ggg agc cgc ttc cag act gtg gac tcg agc aac     1239
Glu Gly Thr Gly Ser Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn
            335                 340                 345

att gat gga ttt gtg aac tgc acc aag atc ctg ggc aac ctg gac ttt     1287
Ile Asp Gly Phe Val Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe
        350                 355                 360

ctg atc acc ggc ctc aat gga gac ccc tgg cac aag atc cct gcc ctg     1335
Leu Ile Thr Gly Leu Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu
    365                 370                 375

gac cca gag aag ctc aat gtc ttc cgg aca gta cgg gag atc aca ggt     1383
Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly
380                 385                 390                 395

tac ctg aac atc cag tcc tgg ccg ccc cac atg cac aac ttc agt gtt     1431
Tyr Leu Asn Ile Gln Ser Trp Pro Pro His Met His Asn Phe Ser Val
                400                 405                 410

ttt tcc aat ttg aca acc att gga ggc aga agc ctc tac aac cgg ggc     1479
Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly
            415                 420                 425

ttc tca ttg ttg atc atg aag aac ttg aat gtc aca tct ctg ggc ttc     1527
Phe Ser Leu Leu Ile Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe
        430                 435                 440

cga tcc ctg aag gaa att agt gct ggg cgt atc tat ata agt gcc aat     1575
Arg Ser Leu Lys Glu Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn
    445                 450                 455

agg cag ctc tgc tac cac cac tct ttg aac tgg acc aag gtg ctt cgg     1623
Arg Gln Leu Cys Tyr His His Ser Leu Asn Trp Thr Lys Val Leu Arg
```

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460                 465                 470                 475

ggg cct acg gaa gag cga cta gac atc aag cat aat cgg ccg cgc aga     1671
Gly Pro Thr Glu Glu Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg
                480                 485                 490

gac tgc gtg gca gag ggc aaa gtg tgt gac cca ctg tgc tcc tct ggg     1719
Asp Cys Val Ala Glu Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly
            495                 500                 505

gga tgc tgg ggc cca ggc cct ggt cag tgc ttg tcc tgt cga aat tat     1767
Gly Cys Trp Gly Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr
        510                 515                 520

agc cga gga ggt gtc tgt gtg acc cac tgc aac ttt ctg aat ggg gag     1815
Ser Arg Gly Gly Val Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu
    525                 530                 535

cct cga gaa ttt gcc cat gag gcc gaa tgc ttc tcc tgc cac ccg gaa     1863
Pro Arg Glu Phe Ala His Glu Ala Glu Cys Phe Ser Cys His Pro Glu
540                 545                 550                 555

tgc caa ccc atg gag ggc act gcc aca tgc aat ggc tcg ggc tct gat     1911
Cys Gln Pro Met Glu Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp
                560                 565                 570

act tgt gct caa tgt gcc cat ttt cga gat ggg ccc cac tgt gtg agc     1959
Thr Cys Ala Gln Cys Ala His Phe Arg Asp Gly Pro His Cys Val Ser
            575                 580                 585

agc tgc ccc cat gga gtc cta ggt gcc aag ggc cca atc tac aag tac     2007
Ser Cys Pro His Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr
        590                 595                 600

cca gat gtt cag aat gaa tgt cgg ccc tgc cat gag aac tgc acc cag     2055
Pro Asp Val Gln Asn Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln
    605                 610                 615

ggg tgt aaa gga cca gag ctt caa gac tgt tta gga caa aca ctg gtg     2103
Gly Cys Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val
620                 625                 630                 635

ctg atc ggc aaa acc cat ctg aca atg gct ttg aca gtg ata gca gga     2151
Leu Ile Gly Lys Thr His Leu Thr Met Ala Leu Thr Val Ile Ala Gly
                640                 645                 650

ttg gta gtg att ttc atg atg ctg ggc ggc act ttt ctc tac tgg cgt     2199
Leu Val Val Ile Phe Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg
            655                 660                 665

ggg cgc cgg att cag aat aaa agg gct atg agg cga tac ttg gaa cgg     2247
Gly Arg Arg Ile Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg
        670                 675                 680

ggt gag agc ata gag cct ctg gac ccc agt gag aag gct aac aaa gtc     2295
Gly Glu Ser Ile Glu Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val
    685                 690                 695

ttg gcc aga atc ttc aaa gag aca gag cta agg aag ctt aaa gtg ctt     2343
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Leu Ala Arg Ile Phe Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu
700                 705                 710                 715

ggc tcg ggt gtc ttt gga act gtg cac aaa gga gtg tgg atc cct gag     2391
Gly Ser Gly Val Phe Gly Thr Val His Lys Gly Val Trp Ile Pro Glu
                720                 725                 730

ggt gaa tca atc aag att cca gtc tgc att aaa gtc att gag gac aag     2439
Gly Glu Ser Ile Lys Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys
            735                 740                 745

agt gga cgg cag agt ttt caa gct gtg aca gat cat atg ctg gcc att     2487
Ser Gly Arg Gln Ser Phe Gln Ala Val Thr Asp His Met Leu Ala Ile
        750                 755                 760

ggc agc ctg gac cat gcc cac att gta agg ctg ctg gga cta tgc cca     2535
Gly Ser Leu Asp His Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro
    765                 770                 775

ggg tca tct ctg cag ctt gtc act caa tat ttg cct ctg ggt tct ctg     2583
Gly Ser Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu
780                 785                 790                 795

ctg gat cat gtg aga caa cac cgg ggg gca ctg ggg cca cag ctg ctg     2631
Leu Asp His Val Arg Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu
                800                 805                 810

ctc aac tgg gga gta caa att gcc aag gga atg tac tac ctt gag gaa     2679
Leu Asn Trp Gly Val Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu
            815                 820                 825

cat ggt atg gtg cat aga aac ctg gct gcc cga aac gtg cta ctc aag     2727
His Gly Met Val His Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys
        830                 835                 840

tca ccc agt cag gtt cag gtg gca gat ttt ggt gtg gct gac ctg ctg     2775
Ser Pro Ser Gln Val Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu
    845                 850                 855

cct cct gat gat aag cag ctg cta tac agt gag gcc aag act cca att     2823
Pro Pro Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile
860                 865                 870                 875

aag tgg atg gcc ctt gag agt atc cac ttt ggg aaa tac aca cac cag     2871
Lys Trp Met Ala Leu Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln
                880                 885                 890

agt gat gtc tgg agc tat ggt gtg aca gtt tgg gag ttg atg acc ttc     2919
Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe
            895                 900                 905

ggg gca gag ccc tat gca ggg cta cga ttg gct gaa gta cca gac ctg     2967
Gly Ala Glu Pro Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu
        910                 915                 920

cta gag aag ggg gag cgg ttg gca cag ccc cag atc tgc aca att gat     3015
Leu Glu Lys Gly Glu Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp
    925                 930                 935
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gtc tac atg gtg atg gtc aag tgt tgg atg att gat gag aac att cgc     3063
Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg
940                 945                 950                 955

cca acc ttt aaa gaa cta gcc aat gag ttc acc agg atg gcc cga gac     3111
Pro Thr Phe Lys Glu Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp
                960                 965                 970

cca cca cgg tat ctg gtc ata aag aga gag agt ggg cct gga ata gcc     3159
Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala
            975                 980                 985

cct ggg cca gag ccc cat ggt ctg aca aac aag aag cta  gag gaa gta    3207
Pro Gly Pro Glu Pro His Gly Leu Thr Asn Lys Lys Leu  Glu Glu Val
        990                 995                 1000

gag ctg  gag cca gaa cta gac  cta gac cta gac ttg  gaa gca gag      3252
Glu Leu  Glu Pro Glu Leu Asp  Leu Asp Leu Asp Leu  Glu Ala Glu
    1005                1010                1015

gag gac  aac ctg gca acc acc  aca ctg ggc tcc gcc  ctc agc cta      3297
Glu Asp  Asn Leu Ala Thr Thr  Thr Leu Gly Ser Ala  Leu Ser Leu
    1020                1025                1030

cca gtt  gga aca ctt aat cgg  cca cgt ggg agc cag  agc ctt tta      3342
Pro Val  Gly Thr Leu Asn Arg  Pro Arg Gly Ser Gln  Ser Leu Leu
    1035                1040                1045

agt cca  tca tct gga tac atg  ccc atg aac cag ggt  aat ctt ggg      3387
Ser Pro  Ser Ser Gly Tyr Met  Pro Met Asn Gln Gly  Asn Leu Gly
    1050                1055                1060

ggg tct  tgc cag gag tct gca  gtt tct ggg agc agt  gaa cgg tgc      3432
Gly Ser  Cys Gln Glu Ser Ala  Val Ser Gly Ser Ser  Glu Arg Cys
    1065                1070                1075

ccc cgt  cca gtc tct cta cac  cca atg cca cgg gga  tgc ctg gca      3477
Pro Arg  Pro Val Ser Leu His  Pro Met Pro Arg Gly  Cys Leu Ala
    1080                1085                1090

tca gag  tca tca gag ggg cat  gta aca ggc tct gag  gct gag ctc      3522
Ser Glu  Ser Ser Glu Gly His  Val Thr Gly Ser Glu  Ala Glu Leu
    1095                1100                1105

cag gag  aaa gtg tca atg tgt  aga agc cgg agc agg  agc cgg agc      3567
Gln Glu  Lys Val Ser Met Cys  Arg Ser Arg Ser Arg  Ser Arg Ser
    1110                1115                1120

cca cgg  cca cgc gga gat agc  gcc tac cat tcc cag  cgc cac agt      3612
Pro Arg  Pro Arg Gly Asp Ser  Ala Tyr His Ser Gln  Arg His Ser
    1125                1130                1135

ctg ctg  act cct gtt acc cca  ctc tcc cca ccc ggg  tta gag gaa      3657
Leu Leu  Thr Pro Val Thr Pro  Leu Ser Pro Pro Gly  Leu Glu Glu
    1140                1145                1150

gag gat  gtc aac ggt tat gtc  atg cca gat aca cac  ctc aaa ggt      3702
Glu Asp  Val Asn Gly Tyr Val  Met Pro Asp Thr His  Leu Lys Gly
    1155                1160                1165
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act ccc tcc tcc cgg gaa ggc acc ctt tct tca gtg ggt ctc agt 3747
Thr Pro Ser Ser Arg Glu Gly Thr Leu Ser Ser Val Gly Leu Ser
1170 1175 1180

tct gtc ctg ggt act gaa gaa gaa gat gaa gat gag gag tat gaa 3792
Ser Val Leu Gly Thr Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu
1185 1190 1195

tac atg aac cgg agg aga agg cac agt cca cct cat ccc cct agg 3837
Tyr Met Asn Arg Arg Arg Arg His Ser Pro Pro His Pro Pro Arg
1200 1205 1210

cca agt tcc ctt gag gag ctg ggt tat gag tac atg gat gtg ggg 3882
Pro Ser Ser Leu Glu Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly
1215 1220 1225

tca gac ctc agt gcc tct ctg ggc agc aca cag agt tgc cca ctc 3927
Ser Asp Leu Ser Ala Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu
1230 1235 1240

cac cct gta ccc atc atg ccc act gca ggc aca act cca gat gaa 3972
His Pro Val Pro Ile Met Pro Thr Ala Gly Thr Thr Pro Asp Glu
1245 1250 1255

gac tat gaa tat atg aat cgg caa cga gat gga ggt ggt cct ggg 4017
Asp Tyr Glu Tyr Met Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly
1260 1265 1270

ggt gat tat gca gcc atg ggg gcc tgc cca gca tct gag caa ggg 4062
Gly Asp Tyr Ala Ala Met Gly Ala Cys Pro Ala Ser Glu Gln Gly
1275 1280 1285

tat gaa gag atg aga gct ttt cag ggg cct gga cat cag gcc ccc 4107
Tyr Glu Glu Met Arg Ala Phe Gln Gly Pro Gly His Gln Ala Pro
1290 1295 1300

cat gtc cat tat gcc cgc cta aaa act cta cgt agc tta gag gct 4152
His Val His Tyr Ala Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala
1305 1310 1315

aca gac tct gcc ttt gat aac cct gat tac tgg cat agc agg ctt 4197
Thr Asp Ser Ala Phe Asp Asn Pro Asp Tyr Trp His Ser Arg Leu
1320 1325 1330

ttc ccc aag gct aat gcc cag aga acg taa ctcctgctcc ctgtggcact 4247
Phe Pro Lys Ala Asn Ala Gln Arg Thr
1335 1340

cagggagcat ttaatggcag ctagtgcctt tagagggtac cgtcttctcc ctattccctc 4307

tctctcccag gtcccagccc cttttcccca gtcccagaca attccattca atctttggag 4367

gcttttaaac attttgacac aaaattctta tggtatgtag ccagctgtgc actttcttct 4427

ctttcccaac cccaggaaag gttttcctta ttttgtgtgc tttcccagtc ccattcctca 4487

gcttcttcac aggcactcct ggagatatga aggattactc tccatatccc ttcctctcag 4547

gctcttgact acttggaact aggctcttat gtgtgccttt gtttcccatc agactgtcaa 4607

gaagaggaaa gggaggaaac ctagcagagg aaagtgtaat tttggtttat gactcttaac 4667

cccctagaaa gacagaagct taaaatctgt gaagaaagag gttaggagta gatattgatt 4727

actatcataa ttcagcactt aactatgagc caggcatcat actaaacttc acctacatta 4787

tctcacttag tcctttatca tccttaaaac aattctgtga catacatatt atctcatttt 4847

acacaaaggg aagtcgggca tggtggctca tgcctgtaat ctcagcactt tgggaggctg 4907

aggcagaagg attacctgag gcaaggagtt tgagaccagc ttagccaaca tagtaagacc 4967

cccatctc 4975

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Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly Leu Leu Phe Ser Leu
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Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr
20 25 30

Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr
35 40 45

Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu
50 55 60

Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile
65 70 75 80

Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr
85 90 95

Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp
100 105 110

Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser
115 120 125

His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser
130 135 140

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Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr
145                 150                 155                 160

Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val
                165                 170                 175

Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly
            180                 185                 190

Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr
        195                 200                 205

Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn
    210                 215                 220

Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp
225                 230                 235                 240

Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val
                245                 250                 255

Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu
            260                 265                 270

Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala
        275                 280                 285

Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala
    290                 295                 300

Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys
305                 310                 315                 320

Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser
                325                 330                 335

Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val
            340                 345                 350

Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu
        355                 360                 365

Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu
    370                 375                 380
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Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly Tyr Leu Asn Ile Gln
385                 390                 395                 400

Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr
                405                 410                 415

Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile
            420                 425                 430

Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe Arg Ser Leu Lys Glu
        435                 440                 445

Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln Leu Cys Tyr
    450                 455                 460

His His Ser Leu Asn Trp Thr Lys Val Leu Arg Gly Pro Thr Glu Glu
465                 470                 475                 480

Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg Asp Cys Val Ala Glu
                485                 490                 495

Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro
            500                 505                 510

Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Gly Gly Val
        515                 520                 525

Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu Pro Arg Glu Phe Ala
    530                 535                 540

His Glu Ala Glu Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Glu
545                 550                 555                 560

Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp Thr Cys Ala Gln Cys
                565                 570                 575

Ala His Phe Arg Asp Gly Pro His Cys Val Ser Ser Cys Pro His Gly
            580                 585                 590

Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Val Gln Asn
        595                 600                 605

Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro
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610 615 620

Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val Leu Ile Gly Lys Thr
625 630 635 640

His Leu Thr Met Ala Leu Thr Val Ile Ala Gly Leu Val Val Ile Phe
645 650 655

Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln
660 665 670

Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu
675 680 685

Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe
690 695 700

Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe
705 710 715 720

Gly Thr Val His Lys Gly Val Trp Ile Pro Glu Gly Glu Ser Ile Lys
725 730 735

Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser
740 745 750

Phe Gln Ala Val Thr Asp His Met Leu Ala Ile Gly Ser Leu Asp His
755 760 765

Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln
770 775 780

Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg
785 790 795 800

Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val
805 810 815

Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Gly Met Val His
820 825 830

Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys Ser Pro Ser Gln Val
835 840 845

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Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys
    850                 855                 860

Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu
865                 870                 875                 880

Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser
                885                 890                 895

Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr
            900                 905                 910

Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu Leu Glu Lys Gly Glu
        915                 920                 925

Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met
    930                 935                 940

Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu
945                 950                 955                 960

Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu
                965                 970                 975

Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro
            980                 985                 990

His Gly Leu Thr Asn Lys Lys Leu  Glu Glu Val Glu Leu  Glu Pro Glu
        995                 1000                1005

Leu Asp  Leu Asp Leu Asp Leu  Glu Ala Glu Glu Asp  Asn Leu Ala
    1010                1015                1020

Thr Thr  Thr Leu Gly Ser Ala  Leu Ser Leu Pro Val  Gly Thr Leu
    1025                1030                1035

Asn Arg  Pro Arg Gly Ser Gln  Ser Leu Leu Ser Pro  Ser Ser Gly
    1040                1045                1050

Tyr Met  Pro Met Asn Gln Gly  Asn Leu Gly Gly Ser  Cys Gln Glu
    1055                1060                1065

Ser Ala  Val Ser Gly Ser Ser  Glu Arg Cys Pro Arg  Pro Val Ser
    1070                1075                1080
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Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu
1085 1090 1095

Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser
1100 1105 1110

Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly
1115 1120 1125

Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val
1130 1135 1140

Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly
1145 1150 1155

Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg
1160 1165 1170

Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr
1175 1180 1185

Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg
1190 1195 1200

Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu
1205 1210 1215

Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala
1220 1225 1230

Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile
1235 1240 1245

Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met
1250 1255 1260

Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala
1265 1270 1275

Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg
1280 1285 1290

Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala
1295 1300 1305

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Arg Leu  Lys Thr Leu Arg Ser  Leu Glu Ala Thr Asp  Ser Ala Phe
    1310                  1315                  1320

Asp Asn  Pro Asp Tyr Trp His  Ser Arg Leu Phe Pro  Lys Ala Asn
    1325                  1330                  1335

Ala Gln  Arg Thr
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aattgtcagc acgggatctg agacttccaa aaa atg aag ccg gcg aca gga ctt      54
                                      Met Lys Pro Ala Thr Gly Leu
                                      1               5

tgg gtc tgg gtg agc ctt ctc gtg gcg gcg ggg acc gtc cag ccc agc     102
Trp Val Trp Val Ser Leu Leu Val Ala Ala Gly Thr Val Gln Pro Ser
        10                  15                  20

gat tct cag tca gtg tgt gca gga acg gag aat aaa ctg agc tct ctc     150
Asp Ser Gln Ser Val Cys Ala Gly Thr Glu Asn Lys Leu Ser Ser Leu
    25                  30                  35

tct gac ctg gaa cag cag tac cga gcc ttg cgc aag tac tat gaa aac     198
Ser Asp Leu Glu Gln Gln Tyr Arg Ala Leu Arg Lys Tyr Tyr Glu Asn
40                  45                  50                  55

tgt gag gtt gtc atg ggc aac ctg gag ata acc agc att gag cac aac     246
Cys Glu Val Val Met Gly Asn Leu Glu Ile Thr Ser Ile Glu His Asn
                60                  65                  70

cgg gac ctc tcc ttc ctg cgg tct gtt cga gaa gtc aca ggc tac gtg     294
Arg Asp Leu Ser Phe Leu Arg Ser Val Arg Glu Val Thr Gly Tyr Val
            75                  80                  85

tta gtg gct ctt aat cag ttt cgt tac ctg cct ctg gag aat tta cgc     342
Leu Val Ala Leu Asn Gln Phe Arg Tyr Leu Pro Leu Glu Asn Leu Arg
        90                  95                  100

att att cgt ggg aca aaa ctt tat gag gat cga tat gcc ttg gca ata     390
Ile Ile Arg Gly Thr Lys Leu Tyr Glu Asp Arg Tyr Ala Leu Ala Ile
    105                 110                 115

ttt tta aac tac aga aaa gat gga aac ttt gga ctt caa gaa ctt gga     438
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Phe Leu Asn Tyr Arg Lys Asp Gly Asn Phe Gly Leu Gln Glu Leu Gly
120                 125                 130                 135

tta aag aac ttg aca gaa atc cta aat ggt gga gtc tat gta gac cag      486
Leu Lys Asn Leu Thr Glu Ile Leu Asn Gly Gly Val Tyr Val Asp Gln
                140                 145                 150

aac aaa ttc ctt tgt tat gca gac acc att cat tgg caa gat att gtt      534
Asn Lys Phe Leu Cys Tyr Ala Asp Thr Ile His Trp Gln Asp Ile Val
            155                 160                 165

cgg aac cca tgg cct tcc aac ttg act ctt gtg tca aca aat ggt agt      582
Arg Asn Pro Trp Pro Ser Asn Leu Thr Leu Val Ser Thr Asn Gly Ser
        170                 175                 180

tca gga tgt gga cgt tgc cat aag tcc tgt act ggc cgt tgc tgg gga      630
Ser Gly Cys Gly Arg Cys His Lys Ser Cys Thr Gly Arg Cys Trp Gly
    185                 190                 195

ccc aca gaa aat cat tgc cag act ttg aca agg acg gtg tgt gca gaa      678
Pro Thr Glu Asn His Cys Gln Thr Leu Thr Arg Thr Val Cys Ala Glu
200                 205                 210                 215

caa tgt gac ggc aga tgc tac gga cct tac gtc agt gac tgc tgc cat      726
Gln Cys Asp Gly Arg Cys Tyr Gly Pro Tyr Val Ser Asp Cys Cys His
                220                 225                 230

cga gaa tgt gct gga ggc tgc tca gga cct aag gac aca gac tgc ttt      774
Arg Glu Cys Ala Gly Gly Cys Ser Gly Pro Lys Asp Thr Asp Cys Phe
            235                 240                 245

gcc tgc atg aat ttc aat gac agt gga gca tgt gtt act cag tgt ccc      822
Ala Cys Met Asn Phe Asn Asp Ser Gly Ala Cys Val Thr Gln Cys Pro
        250                 255                 260

caa acc ttt gtc tac aat cca acc acc ttt caa ctg gag cac aat ttc      870
Gln Thr Phe Val Tyr Asn Pro Thr Thr Phe Gln Leu Glu His Asn Phe
    265                 270                 275

aat gca aag tac aca tat gga gca ttc tgt gtc aag aaa tgt cca cat      918
Asn Ala Lys Tyr Thr Tyr Gly Ala Phe Cys Val Lys Lys Cys Pro His
280                 285                 290                 295

aac ttt gtg gta gat tcc agt tct tgt gtg cgt gcc tgc cct agt tcc      966
Asn Phe Val Val Asp Ser Ser Ser Cys Val Arg Ala Cys Pro Ser Ser
                300                 305                 310

aag atg gaa gta gaa gaa aat ggg att aaa atg tgt aaa cct tgc act     1014
Lys Met Glu Val Glu Glu Asn Gly Ile Lys Met Cys Lys Pro Cys Thr
            315                 320                 325

gac att tgc cca aaa gct tgt gat ggc att ggc aca gga tca ttg atg     1062
Asp Ile Cys Pro Lys Ala Cys Asp Gly Ile Gly Thr Gly Ser Leu Met
        330                 335                 340

tca gct cag act gtg gat tcc agt aac att gac aaa ttc ata aac tgt     1110
Ser Ala Gln Thr Val Asp Ser Ser Asn Ile Asp Lys Phe Ile Asn Cys
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acc aag atc aat ggg aat ttg atc ttt cta gtc act ggt att cat ggg     1158
Thr Lys Ile Asn Gly Asn Leu Ile Phe Leu Val Thr Gly Ile His Gly
360                 365                 370                 375

gac cct tac aat gca att gaa gcc ata gac cca gag aaa ctg aac gtc     1206
Asp Pro Tyr Asn Ala Ile Glu Ala Ile Asp Pro Glu Lys Leu Asn Val
                380                 385                 390

ttt cgg aca gtc aga gag ata aca ggt ttc ctg aac ata cag tca tgg     1254
Phe Arg Thr Val Arg Glu Ile Thr Gly Phe Leu Asn Ile Gln Ser Trp
            395                 400                 405

cca cca aac atg act gac ttc agt gtt ttt tct aac ctg gtg acc att     1302
Pro Pro Asn Met Thr Asp Phe Ser Val Phe Ser Asn Leu Val Thr Ile
        410                 415                 420

ggt gga aga gta ctc tat agt ggc ctg tcc ttg ctt atc ctc aag caa     1350
Gly Gly Arg Val Leu Tyr Ser Gly Leu Ser Leu Leu Ile Leu Lys Gln
    425                 430                 435

cag ggc atc acc tct cta cag ttc cag tcc ctg aag gaa atc agc gca     1398
Gln Gly Ile Thr Ser Leu Gln Phe Gln Ser Leu Lys Glu Ile Ser Ala
440                 445                 450                 455

gga aac atc tat att act gac aac agc aac ctg tgt tat tat cat acc     1446
Gly Asn Ile Tyr Ile Thr Asp Asn Ser Asn Leu Cys Tyr Tyr His Thr
                460                 465                 470

att aac tgg aca aca ctc ttc agc aca atc aac cag aga ata gta atc     1494
Ile Asn Trp Thr Thr Leu Phe Ser Thr Ile Asn Gln Arg Ile Val Ile
            475                 480                 485

cgg gac aac aga aaa gct gaa aat tgt act gct gaa gga atg gtg tgc     1542
Arg Asp Asn Arg Lys Ala Glu Asn Cys Thr Ala Glu Gly Met Val Cys
        490                 495                 500

aac cat ctg tgt tcc agt gat ggc tgt tgg gga cct ggg cca gac caa     1590
Asn His Leu Cys Ser Ser Asp Gly Cys Trp Gly Pro Gly Pro Asp Gln
    505                 510                 515

tgt ctg tcg tgt cgc cgc ttc agt aga gga agg atc tgc ata gag tct     1638
Cys Leu Ser Cys Arg Arg Phe Ser Arg Gly Arg Ile Cys Ile Glu Ser
520                 525                 530                 535

tgt aac ctc tat gat ggt gaa ttt cgg gag ttt gag aat ggc tcc atc     1686
Cys Asn Leu Tyr Asp Gly Glu Phe Arg Glu Phe Glu Asn Gly Ser Ile
                540                 545                 550

tgt gtg gag tgt gac ccc cag tgt gag aag atg gaa gat ggc ctc ctc     1734
Cys Val Glu Cys Asp Pro Gln Cys Glu Lys Met Glu Asp Gly Leu Leu
            555                 560                 565

aca tgc cat gga ccg ggt cct gac aac tgt aca aag tgc tct cat ttt     1782
Thr Cys His Gly Pro Gly Pro Asp Asn Cys Thr Lys Cys Ser His Phe
        570                 575                 580

aaa gat ggc cca aac tgt gtg gaa aaa tgt cca gat ggc tta cag ggg     1830
Lys Asp Gly Pro Asn Cys Val Glu Lys Cys Pro Asp Gly Leu Gln Gly
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gca aac agt ttc att ttc aag tat gct gat cca gat cgg gag tgc cac     1878
Ala Asn Ser Phe Ile Phe Lys Tyr Ala Asp Pro Asp Arg Glu Cys His
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cca tgc cat cca aac tgc acc caa ggg tgt aac ggt ccc act agt cat     1926
Pro Cys His Pro Asn Cys Thr Gln Gly Cys Asn Gly Pro Thr Ser His
                620                 625                 630

gac tgc att tac tac cca tgg acg ggc cat tcc act tta cca caa cat     1974
Asp Cys Ile Tyr Tyr Pro Trp Thr Gly His Ser Thr Leu Pro Gln His
            635                 640                 645

gct aga act ccc ctg att gca gct gga gta att ggt ggg ctc ttc att     2022
Ala Arg Thr Pro Leu Ile Ala Ala Gly Val Ile Gly Gly Leu Phe Ile
        650                 655                 660

ctg gtc att gtg ggt ctg aca ttt gct gtt tat gtt aga agg aag agc     2070
Leu Val Ile Val Gly Leu Thr Phe Ala Val Tyr Val Arg Arg Lys Ser
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atc aaa aag aaa aga gcc ttg aga aga ttc ttg gaa aca gag ttg gtg     2118
Ile Lys Lys Lys Arg Ala Leu Arg Arg Phe Leu Glu Thr Glu Leu Val
680                 685                 690                 695

gaa cca tta act ccc agt ggc aca gca ccc aat caa gct caa ctt cgt     2166
Glu Pro Leu Thr Pro Ser Gly Thr Ala Pro Asn Gln Ala Gln Leu Arg
                700                 705                 710

att ttg aaa gaa act gag ctg aag agg gta aaa gtc ctt ggc tca ggt     2214
Ile Leu Lys Glu Thr Glu Leu Lys Arg Val Lys Val Leu Gly Ser Gly
            715                 720                 725

gct ttt gga acg gtt tat aaa ggt att tgg gta cct gaa gga gaa act     2262
Ala Phe Gly Thr Val Tyr Lys Gly Ile Trp Val Pro Glu Gly Glu Thr
        730                 735                 740

gtg aag att cct gtg gct att aag att ctt aat gag aca act ggt ccc     2310
Val Lys Ile Pro Val Ala Ile Lys Ile Leu Asn Glu Thr Thr Gly Pro
    745                 750                 755

aag gca aat gtg gag ttc atg gat gaa gct ctg atc atg gca agt atg     2358
Lys Ala Asn Val Glu Phe Met Asp Glu Ala Leu Ile Met Ala Ser Met
760                 765                 770                 775

gat cat cca cac cta gtc cgg ttg ctg ggt gtg tgt ctg agc cca acc     2406
Asp His Pro His Leu Val Arg Leu Leu Gly Val Cys Leu Ser Pro Thr
                780                 785                 790

atc cag ctg gtt act caa ctt atg ccc cat ggc tgc ctg ttg gag tat     2454
Ile Gln Leu Val Thr Gln Leu Met Pro His Gly Cys Leu Leu Glu Tyr
            795                 800                 805

gtc cac gag cac aag gat aac att gga tca caa ctg ctg ctt aac tgg     2502
Val His Glu His Lys Asp Asn Ile Gly Ser Gln Leu Leu Leu Asn Trp
        810                 815                 820

tgt gtc cag ata gct aag gga atg atg tac ctg gaa gaa aga cga ctc     2550
Cys Val Gln Ile Ala Lys Gly Met Met Tyr Leu Glu Glu Arg Arg Leu
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gtt cat cgg gat ttg gca gcc cgt aat gtc tta gtg aaa tct cca aac     2598
Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Ser Pro Asn
840                 845                 850                 855

cat gtg aaa atc aca gat ttt ggg cta gcc aga ctc ttg gaa gga gat     2646
His Val Lys Ile Thr Asp Phe Gly Leu Ala Arg Leu Leu Glu Gly Asp
                860                 865                 870

gaa aaa gag tac aat gct gat gga gga aag atg cca att aaa tgg atg     2694
Glu Lys Glu Tyr Asn Ala Asp Gly Gly Lys Met Pro Ile Lys Trp Met
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Trp Ser Tyr Gly Val Thr Ile Trp Glu Leu Met Thr Phe Gly Gly Lys
    905                 910                 915

ccc tat gat gga att cca acg cga gaa atc cct gat tta tta gag aaa     2838
Pro Tyr Asp Gly Ile Pro Thr Arg Glu Ile Pro Asp Leu Leu Glu Lys
920                 925                 930                 935

gga gaa cgt ttg cct cag cct ccc atc tgc act att gac gtt tac atg     2886
Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr Met
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gtc atg gtc aaa tgt tgg atg att gat gct gac agt aga cct aaa ttt     2934
Val Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys Phe
            955                 960                 965

aag gaa ctg gct gct gag ttt tca agg atg gct cga gac cct caa aga     2982
Lys Glu Leu Ala Ala Glu Phe Ser Arg Met Ala Arg Asp Pro Gln Arg
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tac cta gtt att cag ggt gat gat cgt atg aag ctt ccc agt cca aat     3030
Tyr Leu Val Ile Gln Gly Asp Asp Arg Met Lys Leu Pro Ser Pro Asn
    985                 990                 995

gac  agc aag ttc ttt cag  aat ctc ttg gat gaa  gag gat ttg gaa     3075
Asp  Ser Lys Phe Phe Gln  Asn Leu Leu Asp Glu  Glu Asp Leu Glu
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gat  atg atg gat gct gag  gag tac ttg gtc cct  cag gct ttc aac     3120
Asp  Met Met Asp Ala Glu  Glu Tyr Leu Val Pro  Gln Ala Phe Asn
1015                1020                1025

atc  cca cct ccc atc tat  act tcc aga gca aga  att gac tcg aat     3165
Ile  Pro Pro Pro Ile Tyr  Thr Ser Arg Ala Arg  Ile Asp Ser Asn
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agg  agt gaa att gga cac  agc cct cct cct gcc  tac acc ccc atg     3210
Arg  Ser Glu Ile Gly His  Ser Pro Pro Pro Ala  Tyr Thr Pro Met
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tca  gga aac cag ttt gta  tac cga gat gga ggt  ttt gct gct gaa     3255
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Gln  Gly Val Ser Val Pro  Tyr Arg Ala Pro Thr  Ser Thr Ile Pro
1075                1080                1085

gaa  gct cct gtg gca cag  ggt gct act gct gag  att ttt gat gac      3345
Glu  Ala Pro Val Ala Gln  Gly Ala Thr Ala Glu  Ile Phe Asp Asp
1090                1095                1100

tcc  tgc tgt aat ggc acc  cta cgc aag cca gtg  gca ccc cat gtc      3390
Ser  Cys Cys Asn Gly Thr  Leu Arg Lys Pro Val  Ala Pro His Val
1105                1110                1115

caa  gag gac agt agc acc  cag agg tac agt gct  gac ccc acc gtg      3435
Gln  Glu Asp Ser Ser Thr  Gln Arg Tyr Ser Ala  Asp Pro Thr Val
1120                1125                1130

ttt  gcc cca gaa cgg agc  cca cga gga gag ctg  gat gag gaa ggt      3480
Phe  Ala Pro Glu Arg Ser  Pro Arg Gly Glu Leu  Asp Glu Glu Gly
1135                1140                1145

tac  atg act cct atg cga  gac aaa ccc aaa caa  gaa tac ctg aat      3525
Tyr  Met Thr Pro Met Arg  Asp Lys Pro Lys Gln  Glu Tyr Leu Asn
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cca  gtg gag gag aac cct  ttt gtt tct cgg aga  aaa aat gga gac      3570
Pro  Val Glu Glu Asn Pro  Phe Val Ser Arg Arg  Lys Asn Gly Asp
1165                1170                1175

ctt  caa gca ttg gat aat  ccc gaa tat cac aat  gca tcc aat ggt      3615
Leu  Gln Ala Leu Asp Asn  Pro Glu Tyr His Asn  Ala Ser Asn Gly
1180                1185                1190

cca  ccc aag gcc gag gat  gag tat gtg aat gag  cca ctg tac ctc      3660
Pro  Pro Lys Ala Glu Asp  Glu Tyr Val Asn Glu  Pro Leu Tyr Leu
1195                1200                1205

aac  acc ttt gcc aac acc  ttg gga aaa gct gag  tac ctg aag aac      3705
Asn  Thr Phe Ala Asn Thr  Leu Gly Lys Ala Glu  Tyr Leu Lys Asn
1210                1215                1220

aac  ata ctg tca atg cca  gag aag gcc aag aaa  gcg ttt gac aac      3750
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cct  gac tac tgg aac cac  agc ctg cca cct cgg  agc acc ctt cag      3795
Pro  Asp Tyr Trp Asn His  Ser Leu Pro Pro Arg  Ser Thr Leu Gln
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cac  cca gac tac ctg cag  gag tac agc aca aaa  tat ttt tat aaa      3840
His  Pro Asp Tyr Leu Gln  Glu Tyr Ser Thr Lys  Tyr Phe Tyr Lys
1255                1260                1265

cag  aat ggg cgg atc cgg  cct att gtg gca gag  aat cct gaa tac      3885
Gln  Asn Gly Arg Ile Arg  Pro Ile Val Ala Glu  Asn Pro Glu Tyr
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cct tac aga cac cgg aat act gtg gtg taa gctcagttgt ggtttttag 3980
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Ile Thr Ser Ile Glu His Asn Arg Asp Leu Ser Phe Leu Arg Ser Val
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Arg Glu Val Thr Gly Tyr Val Leu Val Ala Leu Asn Gln Phe Arg Tyr
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Asp Arg Tyr Ala Leu Ala Ile Phe Leu Asn Tyr Arg Lys Asp Gly Asn
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Phe Gly Leu Gln Glu Leu Gly Leu Lys Asn Leu Thr Glu Ile Leu Asn
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Gly Gly Val Tyr Val Asp Gln Asn Lys Phe Leu Cys Tyr Ala Asp Thr
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Ile His Trp Gln Asp Ile Val Arg Asn Pro Trp Pro Ser Asn Leu Thr
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Leu Val Ser Thr Asn Gly Ser Ser Gly Cys Gly Arg Cys His Lys Ser
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Cys Thr Gly Arg Cys Trp Gly Pro Thr Glu Asn His Cys Gln Thr Leu
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Tyr Val Ser Asp Cys Cys His Arg Glu Cys Ala Gly Gly Cys Ser Gly
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Pro Lys Asp Thr Asp Cys Phe Ala Cys Met Asn Phe Asn Asp Ser Gly
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Ala Cys Val Thr Gln Cys Pro Gln Thr Phe Val Tyr Asn Pro Thr Thr
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340 345 350

Ile Asp Lys Phe Ile Asn Cys Thr Lys Ile Asn Gly Asn Leu Ile Phe
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Leu Val Thr Gly Ile His Gly Asp Pro Tyr Asn Ala Ile Glu Ala Ile
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Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly
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Asn Leu Cys Tyr Tyr His Thr Ile Asn Trp Thr Thr Leu Phe Ser Thr
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Trp Gly Pro Gly Pro Asp Gln Cys Leu Ser Cys Arg Arg Phe Ser Arg
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Cys Asn Gly Pro Thr Ser His Asp Cys Ile Tyr Tyr Pro Trp Thr Gly
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His Ser Thr Leu Pro Gln His Ala Arg Thr Pro Leu Ile Ala Ala Gly
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Ser Gln Leu Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Met
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Tyr Leu Glu Glu Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn
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Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe Gly Leu
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Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile His Tyr Arg Lys
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Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Ile Trp Glu
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Cys Thr Ile Asp Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp
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Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile Cys Gly Pro Gly
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Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg Leu Glu Asn Cys
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Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile Ser Lys Ala Glu
        55                  60                  65

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Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val Ile Thr Glu Tyr
    70                  75                  80

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Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu Gly Asp Leu Phe
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ctg gtc atc ttc gag atg acc aat ctc aag gat att ggg ctt tac aac      441
Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile Gly Leu Tyr Asn
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Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu Lys Asn Ala Asp
        135                 140                 145

ctc tgt tac ctc tcc act gtg gac tgg tcc ctg atc ctg gat gcg gtg      537
Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile Leu Asp Ala Val
    150                 155                 160

tcc aat aac tac att gtg ggg aat aag ccc cca aag gaa tgt ggg gac      585
Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys Glu Cys Gly Asp
165                 170                 175                 180

ctg tgt cca ggg acc atg gag gag aag ccg atg tgt gag aag acc acc      633
Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys Glu Lys Thr Thr
                185                 190                 195

atc aac aat gag tac aac tac cgc tgc tgg acc aca aac cgc tgc cag      681
Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr Asn Arg Cys Gln
            200                 205                 210

aaa atg tgc cca agc acg tgt ggg aag cgg gcg tgc acc gag aac aat      729
Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys Thr Glu Asn Asn
        215                 220                 225
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gag tgc tgc cac ccc gag tgc ctg ggc agc tgc agc gcg cct gac aac      777
Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser Ala Pro Asp Asn
    230                 235                 240

gac acg gcc tgt gta gct tgc cgc cac tac tac tat gcc ggt gtc tgt      825
Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr Ala Gly Val Cys
245                 250                 255                 260

gtg cct gcc tgc ccg ccc aac acc tac agg ttt gag ggc tgg cgc tgt      873
Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu Gly Trp Arg Cys
                265                 270                 275

gtg gac cgt gac ttc tgc gcc aac atc ctc agc gcc gag agc agc gac      921
Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala Glu Ser Ser Asp
            280                 285                 290

tcc gag ggg ttt gtg atc cac gac ggc gag tgc atg cag gag tgc ccc      969
Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met Gln Glu Cys Pro
        295                 300                 305

tcg ggc ttc atc cgc aac ggc agc cag agc atg tac tgc atc cct tgt     1017
Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr Cys Ile Pro Cys
    310                 315                 320

gaa ggt cct tgc ccg aag gtc tgt gag gaa gaa aag aaa aca aag acc     1065
Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys Lys Thr Lys Thr
325                 330                 335                 340

att gat tct gtt act tct gct cag atg ctc caa gga tgc acc atc ttc     1113
Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly Cys Thr Ile Phe
                345                 350                 355

aag ggc aat ttg ctc att aac atc cga cgg ggg aat aac att gct tca     1161
Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn Asn Ile Ala Ser
            360                 365                 370

gag ctg gag aac ttc atg ggg ctc atc gag gtg gtg acg ggc tac gtg     1209
Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val Thr Gly Tyr Val
        375                 380                 385

aag atc cgc cat tct cat gcc ttg gtc tcc ttg tcc ttc cta aaa aac     1257
Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser Phe Leu Lys Asn
    390                 395                 400

ctt cgc ctc atc cta gga gag gag cag cta gaa ggg aat tac tcc ttc     1305
Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly Asn Tyr Ser Phe
405                 410                 415                 420

tac gtc ctc gac aac cag aac ttg cag caa ctg tgg gac tgg gac cac     1353
Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp Asp Trp Asp His
                425                 430                 435

cgc aac ctg acc atc aaa gca ggg aaa atg tac ttt gct ttc aat ccc     1401
Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe Ala Phe Asn Pro
            440                 445                 450

aaa tta tgt gtt tcc gaa att tac cgc atg gag gaa gtg acg ggg act     1449
Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu Val Thr Gly Thr
        455                 460                 465
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aaa ggg cgc caa agc aaa ggg gac ata aac acc agg aac aac ggg gag      1497
Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg Asn Asn Gly Glu
    470                 475                 480

aga gcc tcc tgt gaa agt gac gtc ctg cat ttc acc tcc acc acc acg      1545
Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr Ser Thr Thr Thr
485                 490                 495                 500

tcg aag aat cgc atc atc ata acc tgg cac cgg tac cgg ccc cct gac      1593
Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr Arg Pro Pro Asp
                505                 510                 515

tac agg gat ctc atc agc ttc acc gtt tac tac aag gaa gca ccc ttt      1641
Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys Glu Ala Pro Phe
            520                 525                 530

aag aat gtc aca gag tat gat ggg cag gat gcc tgc ggc tcc aac agc      1689
Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser
        535                 540                 545

tgg aac atg gtg gac gtg gac ctc ccg ccc aac aag gac gtg gag ccc      1737
Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys Asp Val Glu Pro
    550                 555                 560

ggc atc tta cta cat ggg ctg aag ccc tgg act cag tac gcc gtt tac      1785
Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln Tyr Ala Val Tyr
565                 570                 575                 580

gtc aag gct gtg acc ctc acc atg gtg gag aac gac cat atc cgt ggg      1833
Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp His Ile Arg Gly
                585                 590                 595

gcc aag agt gag atc ttg tac att cgc acc aat gct tca gtt cct tcc      1881
Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala Ser Val Pro Ser
            600                 605                 610

att ccc ttg gac gtt ctt tca gca tcg aac tcc tct tct cag tta atc      1929
Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser Ser Gln Leu Ile
        615                 620                 625

gtg aag tgg aac cct ccc tct ctg ccc aac ggc aac ctg agt tac tac      1977
Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn Leu Ser Tyr Tyr
    630                 635                 640

att gtg cgc tgg cag cgg cag cct cag gac ggc tac ctt tac cgg cac      2025
Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr Leu Tyr Arg His
645                 650                 655                 660

aat tac tgc tcc aaa gac aaa atc ccc atc agg aag tat gcc gac ggc      2073
Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys Tyr Ala Asp Gly
                665                 670                 675

acc atc gac att gag gag gtc aca gag aac ccc aag act gag gtg tgt      2121
Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys Thr Glu Val Cys
            680                 685                 690

ggt ggg gag aaa ggg cct tgc tgc gcc tgc ccc aaa act gaa gcc gag      2169
Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys Thr Glu Ala Glu
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695 700 705

aag cag gcc gag aag gag gag gct gaa tac cgc aaa gtc ttt gag aat 2217
Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys Val Phe Glu Asn
710 715 720

ttc ctg cac aac tcc atc ttc gtg ccc aga cct gaa agg aag cgg aga 2265
Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu Arg Lys Arg Arg
725 730 735 740

gat gtc atg caa gtg gcc aac acc acc atg tcc agc cga agc agg aac 2313
Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser Arg Ser Arg Asn
745 750 755

acc acg gcc gca gac acc tac aac atc acc gac ccg gaa gag ctg gag 2361
Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro Glu Glu Leu Glu
760 765 770

aca gag tac cct ttc ttt gag agc aga gtg gat aac aag gag aga act 2409
Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn Lys Glu Arg Thr
775 780 785

gtc att tct aac ctt cgg cct ttc aca ttg tac cgc atc gat atc cac 2457
Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg Ile Asp Ile His
790 795 800

agc tgc aac cac gag gct gag aag ctg ggc tgc agc gcc tcc aac ttc 2505
Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser Ala Ser Asn Phe
805 810 815 820

gtc ttt gca agg act atg ccc gca gaa gga gca gat gac att cct ggg 2553
Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp Asp Ile Pro Gly
825 830 835

cca gtg acc tgg gag cca agg cct gaa aac tcc atc ttt tta aag tgg 2601
Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile Phe Leu Lys Trp
840 845 850

ccg gaa cct gag aat ccc aat gga ttg att cta atg tat gaa ata aaa 2649
Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met Tyr Glu Ile Lys
855 860 865

tac gga tca caa gtt gag gat cag cga gaa tgt gtg tcc aga cag gaa 2697
Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val Ser Arg Gln Glu
870 875 880

tac agg aag tat gga ggg gcc aag cta aac cgg cta aac ccg ggg aac 2745
Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu Asn Pro Gly Asn
885 890 895 900

tac aca gcc cgg att cag gcc aca tct ctc tct ggg aat ggg tcg tgg 2793
Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly Asn Gly Ser Trp
905 910 915

aca gat cct gtg ttc ttc tat gtc cag gcc aaa aca gga tat gaa aac 2841
Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr Gly Tyr Glu Asn
920 925 930

ttc atc cat ctg atc atc gct ctg ccc gtc gct gtc ctg ttg atc gtg 2889

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Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Val Leu Leu Ile Val
        935                 940                 945

gga ggg ttg gtg att atg ctg tac gtc ttc cat aga aag aga aat aac     2937
Gly Gly Leu Val Ile Met Leu Tyr Val Phe His Arg Lys Arg Asn Asn
    950                 955                 960

agc agg ctg ggg aat gga gtg ctg tat gcc tct gtg aac ccg gag tac     2985
Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val Asn Pro Glu Tyr
965                 970                 975                 980

ttc agc gct gct gat gtg tac gtt cct gat gag tgg gag gtg gct cgg     3033
Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp Glu Val Ala Arg
                985                 990                 995

gag aag atc acc  atg agc cgg gaa ctt  ggg cag ggg tcg ttt  ggg      3078
Glu Lys Ile Thr  Met Ser Arg Glu Leu  Gly Gln Gly Ser Phe  Gly
            1000                1005                1010

atg gtc tat gaa  gga gtt gcc aag ggt  gtg gtg aaa gat gaa  cct      3123
Met Val Tyr Glu  Gly Val Ala Lys Gly  Val Val Lys Asp Glu  Pro
            1015                1020                1025

gaa acc aga gtg  gcc att aaa aca gtg  aac gag gcc gca agc  atg      3168
Glu Thr Arg Val  Ala Ile Lys Thr Val  Asn Glu Ala Ala Ser  Met
            1030                1035                1040

cgt gag agg att  gag ttt ctc aac gaa  gct tct gtg atg aag  gag      3213
Arg Glu Arg Ile  Glu Phe Leu Asn Glu  Ala Ser Val Met Lys  Glu
            1045                1050                1055

ttc aat tgt cac  cat gtg gtg cga ttg  ctg ggt gtg gtg tcc  caa      3258
Phe Asn Cys His  His Val Val Arg Leu  Leu Gly Val Val Ser  Gln
            1060                1065                1070

ggc cag cca aca  ctg gtc atc atg gaa  ctg atg aca cgg ggc  gat      3303
Gly Gln Pro Thr  Leu Val Ile Met Glu  Leu Met Thr Arg Gly  Asp
            1075                1080                1085

ctc aaa agt tat  ctc cgg tct ctg agg  cca gaa atg gag aat  aat      3348
Leu Lys Ser Tyr  Leu Arg Ser Leu Arg  Pro Glu Met Glu Asn  Asn
            1090                1095                1100

cca gtc cta gca  cct cca agc ctg agc  aag atg att cag atg  gcc      3393
Pro Val Leu Ala  Pro Pro Ser Leu Ser  Lys Met Ile Gln Met  Ala
            1105                1110                1115

gga gag att gca  gac ggc atg gca tac  ctc aac gcc aat aag  ttc      3438
Gly Glu Ile Ala  Asp Gly Met Ala Tyr  Leu Asn Ala Asn Lys  Phe
            1120                1125                1130

gtc cac aga gac  ctt gct gcc cgg aat  tgc atg gta gcc gaa  gat      3483
Val His Arg Asp  Leu Ala Ala Arg Asn  Cys Met Val Ala Glu  Asp
            1135                1140                1145

ttc aca gtc aaa  atc gga gat ttt ggt  atg acg cga gat atc  tat      3528
Phe Thr Val Lys  Ile Gly Asp Phe Gly  Met Thr Arg Asp Ile  Tyr
            1150                1155                1160
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gag aca gac tat  tac cgg aaa gga ggc  aaa ggg ctg ctg ccc  gtg      3573
Glu Thr Asp Tyr  Tyr Arg Lys Gly Gly  Lys Gly Leu Leu Pro  Val
            1165                 1170                 1175

cgc tgg atg tct  cct gag tcc ctc aag  gat gga gtc ttc acc  act      3618
Arg Trp Met Ser  Pro Glu Ser Leu Lys  Asp Gly Val Phe Thr  Thr
            1180                 1185                 1190

tac tcg gac gtc  tgg tcc ttc ggg gtc  gtc ctc tgg gag atc  gcc      3663
Tyr Ser Asp Val  Trp Ser Phe Gly Val  Val Leu Trp Glu Ile  Ala
            1195                 1200                 1205

aca ctg gcc gag  cag ccc tac cag ggc  ttg tcc aac gag caa  gtc      3708
Thr Leu Ala Glu  Gln Pro Tyr Gln Gly  Leu Ser Asn Glu Gln  Val
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ctt cgc ttc gtc  atg gag ggc ggc ctt  ctg gac aag cca gac  aac      3753
Leu Arg Phe Val  Met Glu Gly Gly Leu  Leu Asp Lys Pro Asp  Asn
            1225                 1230                 1235

tgt cct gac atg  ctg ttt gaa ctg atg  cgc atg tgc tgg cag  tat      3798
Cys Pro Asp Met  Leu Phe Glu Leu Met  Arg Met Cys Trp Gln  Tyr
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aac ccc aag atg  agg cct tcc ttc ctg  gag atc atc agc agc  atc      3843
Asn Pro Lys Met  Arg Pro Ser Phe Leu  Glu Ile Ile Ser Ser  Ile
            1255                 1260                 1265

aaa gag gag atg  gag cct ggc ttc cgg  gag gtc tcc ttc tac  tac      3888
Lys Glu Glu Met  Glu Pro Gly Phe Arg  Glu Val Ser Phe Tyr  Tyr
            1270                 1275                 1280

agc gag gag aac  aag ctg ccc gag ccg  gag gag ctg gac ctg  gag      3933
Ser Glu Glu Asn  Lys Leu Pro Glu Pro  Glu Glu Leu Asp Leu  Glu
            1285                 1290                 1295

cca gag aac atg  gag agc gtc ccc ctg  gac ccc tcg gcc tcc  tcg      3978
Pro Glu Asn Met  Glu Ser Val Pro Leu  Asp Pro Ser Ala Ser  Ser
            1300                 1305                 1310

tcc tcc ctg cca  ctg ccc gac aga cac  tca gga cac aag gcc  gag      4023
Ser Ser Leu Pro  Leu Pro Asp Arg His  Ser Gly His Lys Ala  Glu
            1315                 1320                 1325

aac ggc ccc ggc  cct ggg gtg ctg gtc  ctc cgc gcc agc ttc  gac      4068
Asn Gly Pro Gly  Pro Gly Val Leu Val  Leu Arg Ala Ser Phe  Asp
            1330                 1335                 1340

gag aga cag cct  tac gcc cac atg aac  ggg ggc cgc aag aac  gag      4113
Glu Arg Gln Pro  Tyr Ala His Met Asn  Gly Gly Arg Lys Asn  Glu
            1345                 1350                 1355

cgg gcc ttg ccg  ctg ccc cag tct tcg  acc tgc tga tccttggatc        4159
Arg Ala Leu Pro  Leu Pro Gln Ser Ser  Thr Cys
            1360                 1365

ctgaatctgt gcaaacagta acgtgtgcgc acgcgcagcg gggtgggggg ggagagagag  4219

ttttaacaat ccattcacaa gcctcctgta cctcagtgga tcttcagttc tgcccttgct  4279
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gcccgcggga gacagcttct ctgcagtaaa acacatttgg gatgttcctt ttttcaatat 4339

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20 25 30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile
50 55 60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val
65 70 75 80

Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu
85 90 95

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe
100 105 110

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile
115 120 125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu
130 135 140

Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile
145 150 155 160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys
165 170 175

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys
180 185 190

Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr
195 200 205

Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys
210 215 220

Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser
225 230 235 240

Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr
245 250 255

Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu
260 265 270

Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala
275 280 285

Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met
290 295 300

Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr
305 310 315 320

Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys
325 330 335

Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly

340 345 350

Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn
355 360 365

Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val
370 375 380

Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser
385 390 395 400

Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly
405 410 415

Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp
420 425 430

Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe
435 440 445

Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu
450 455 460

Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg
465 470 475 480

Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr
485 490 495

Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr
500 505 510

Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys
515 520 525

Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys
530 535 540

Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys
545 550 555 560

Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln
565 570 575

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Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp
            580                 585                 590

His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala
        595                 600                 605

Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser
    610                 615                 620

Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn
625                 630                 635                 640

Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
                645                 650                 655

Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
            660                 665                 670

Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys
        675                 680                 685

Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys
    690                 695                 700

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys
705                 710                 715                 720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
                725                 730                 735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser
            740                 745                 750

Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro
        755                 760                 765

Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn
    770                 775                 780

Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg
785                 790                 795                 800

Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser
                805                 810                 815
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Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp
            820                 825                 830

Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile
        835                 840                 845

Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met
    850                 855                 860

Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val
865                 870                 875                 880

Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu
                885                 890                 895

Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly
            900                 905                 910

Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr
        915                 920                 925

Gly Tyr Glu Asn Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Val
    930                 935                 940

Leu Leu Ile Val Gly Gly Leu Val Ile Met Leu Tyr Val Phe His Arg
945                 950                 955                 960

Lys Arg Asn Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val
                965                 970                 975

Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp
            980                 985                 990

Glu Val Ala Arg Glu Lys Ile Thr  Met Ser Arg Glu Leu  Gly Gln Gly
        995                 1000                1005

Ser Phe  Gly Met Val Tyr Glu  Gly Val Ala Lys Gly  Val Val Lys
    1010                1015                1020

Asp Glu  Pro Glu Thr Arg Val  Ala Ile Lys Thr Val  Asn Glu Ala
    1025                1030                1035

Ala Ser  Met Arg Glu Arg Ile  Glu Phe Leu Asn Glu  Ala Ser Val
    1040                1045                1050
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Met Lys Glu Phe Asn Cys His His Val Val Arg Leu Leu Gly Val
1055 1060 1065

Val Ser Gln Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met Thr
1070 1075 1080

Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Met
1085 1090 1095

Glu Asn Asn Pro Val Leu Ala Pro Pro Ser Leu Ser Lys Met Ile
1100 1105 1110

Gln Met Ala Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala
1115 1120 1125

Asn Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val
1130 1135 1140

Ala Glu Asp Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg
1145 1150 1155

Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys Gly Leu
1160 1165 1170

Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu Lys Asp Gly Val
1175 1180 1185

Phe Thr Thr Tyr Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp
1190 1195 1200

Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu Ser Asn
1205 1210 1215

Glu Gln Val Leu Arg Phe Val Met Glu Gly Gly Leu Leu Asp Lys
1220 1225 1230

Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg Met Cys
1235 1240 1245

Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu Ile Ile
1250 1255 1260

Ser Ser Ile Lys Glu Glu Met Glu Pro Gly Phe Arg Glu Val Ser

1265 1270 1275

Phe Tyr Tyr Ser Glu Glu Asn Lys Leu Pro Glu Pro Glu Glu Leu
1280 1285 1290

Asp Leu Glu Pro Glu Asn Met Glu Ser Val Pro Leu Asp Pro Ser
1295 1300 1305

Ala Ser Ser Ser Ser Leu Pro Leu Pro Asp Arg His Ser Gly His
1310 1315 1320

Lys Ala Glu Asn Gly Pro Gly Pro Gly Val Leu Val Leu Arg Ala
1325 1330 1335

Ser Phe Asp Glu Arg Gln Pro Tyr Ala His Met Asn Gly Gly Arg
1340 1345 1350

Lys Asn Glu Arg Ala Leu Pro Leu Pro Gln Ser Ser Thr Cys
1355 1360 1365

<210> 19
<211> 22
<212> DNA
<213> artificial sequence

<220>
<223> exon 8 primer (3' PCR amplification primer; see EXAMPLE I)

<400> 19
aacacagcgg tgtgagaagt gc 22

<210> 20
<211> 28
<212> DNA
<213> artificial sequence

<220>
<223> intron 9 primer (5' PCR amplification primer; see EXAMPLE I)

<400> 20
gtatcggtag ttcatttcct ttggttgc 28

<210> 21
<211> 20
<212> DNA
<213> artificial sequence

<220>
<223> 3' PCR amplification primer for rat intron 8 region

<400> 21
ctacctgtct acggaagtgg 20

<210> 22
<211> 20
<212> DNA
<213> artificial sequence

<220>
<223> 5' PCR amplification primer for rat intron 8 region

<400> 22
ttccgggcag aaatgccagg 20

<210> 23
<211> 419
<212> PRT
<213> Homo sapiens

<400> 23

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

```
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145                 150                 155                 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
                165                 170                 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
            180                 185                 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
        195                 200                 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
    210                 215                 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225                 230                 235                 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
                245                 250                 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
            260                 265                 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
        275                 280                 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
    290                 295                 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305                 310                 315                 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
                325                 330                 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
            340                 345                 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
        355                 360                 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
    370                 375                 380
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Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
405 410 415

Tyr Glu Gly

<210> 24
<211> 79
<212> PRT
<213> Homo sapiens

<400> 24

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75